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LESIONS OF THE PHARYNX IN ACUTE RHEUMATISM

BY

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Within recent years several observers have noted the presence of rheumatic lesions in the neighbourhood of the tonsils.

Shaw[1], in his examination of the tissues from a girl aged 15 who died of rheumatic fever and chorea, found a few Aschoff nodules in the outer layers of the fibrous capsule of the tonsil. There was no evidence of any damage to the nearby fibres of the superior constrictor muscle of the pharynx.

Graff[2] has described rheumatic lesions in the peritonsillar tissues of a man aged 22 who died 16 days from the commencement of a first attack of acute polyarthritis. The essential nature of the lesions was degeneration of the collagen fibres and increase of fibroblasts. Lymphocytes and plasma cells played only a slight part and multinucleated cells were very scarce. Polynuclear cells were seldom seen. The lesions were numerous and were found in the tonsillar capsule and in the connective tissue of the superior constrictor muscles. No damage to muscle tissue was observed.

In the capsule of the left tonsil of Graff's case there was an extensive rheumatic infiltration reaching from the margin of the adenoid tissue deep into the musculature of the tonsil bed. Similar smaller lesions, evidently at an earlier stage of their evolution, were found in the neighbourhood of the right tonsil.

Graff, who considers that the lesion in the left tonsil is the primary one (Primarinfekt), is of the opinion that rheumatic fever is caused by a specific micro-organism—infection passing from the surface of the tonsil to the deeper tissues by way of the lymph stream.

Klinge[3] has confirmed Graff's observations as regards the occurrence of these peritonsillar lesions in the early stages of rheumatic fever, and has also reported their presence in the fibrous tissue at the root of the tongue. Further, Klinge has noticed that the muscle tissue bordering the nodules may show varying degrees of damage, from simple loss of striation to complete necrosis.

Yoshitake[4], who made a more extended examination of the tissues from Graff's case, found the nodules in the upper part of the œsophagus and in the posterior third of the tongue as well as in the tissues of the pharynx generally. They were especially numerous in the posterior wall of the throat. In a second case Yoshitake observed that the rheumatic nodules were present also in the larynx.

Present investigations.—The present report deals with the histological examination of the pharyngeal tissues and the cervical lymph nodes of four patients who died of rheumatic fever uncomplicated by any other disease.

Case 1.—Female, aged 20. Admitted with acute arthritis and heart disease. History of an attack of rheumatic fever two years previously. Has been troubled a great deal with sore throats and is recovering from a severe attack of tonsillitis which began two weeks before admission and before the present severe illness began. Death occurred ten days after admission,

AUTOPSY PROTOCOL. Moderate dilatation and hypertrophy of the heart. Rheumatic pericarditis, myocarditis, and endocarditis of the mitral and aortic valves. No marked fibrosis of the valve leaflets. A few ounces of blood stained fluid in each pleural cavity. Chronic venous congestion of viscera.

HISTOLOGICAL EXAMINATION (Figs. 1—13). The tonsils are large and swollen, with deep wide crypts full of cellular debris, polynuclears, and bacteria, mostly Gram-positive cocci. The germ centres are not conspicuous, and plasma cells are prominent especially at those points where the surface epithelium is ulcerated. In and just beneath the epithelium there is much polynuclear cell infiltration. There is marked proliferation of the endothelial cells, and some of the smaller vessels show a moderate degree of intimal thickening. In the tonsil capsule on both sides there are numerous lesions of rheumatic type. Some are entirely confined to the capsular tissue, but the large majority are situated at the outer edge where the superior constrictor muscle fibres are attached. Here they may be either pushing the muscle aside or infiltrating into the fibrous tissue between the muscle bundles. There is a marked increase in the number of these lesions in the connective tissue of the muscle immediately surrounding the tonsils, and also in the region of the sinus pyriformis where they can be seen in conspicuous numbers in the submucosa as well as in the deeper layers. Further out from the neighbourhood of the tonsils they are not so frequently found, but they again become very numerous towards the upper end of the œsophagus.

There are two distinct forms of the lesion. A small one situated in the fibrous tissue surrounding small or medium sized arteries and identical with the Aschoff nodules of the myocardium (Fig. 1). A more diffuse one which has not the same definite relationship to the vessels and which corresponds more to the changes found in the region of the joints and tendons of rheumatic subjects (Fig. 2 and 3). The diffuse type is more common. Both show the same histological features.

In the earliest stage there is a varying amount of degenerative change of the collagen fibres accompanied by increased proliferation of fibroblasts. The collagen becomes swollen and disintegrated and looks and stains like fibrinous material. Occasionally this collagen necrosis is the predominating feature so that in comparison the fibroblastic proliferation is slight (Fig. 4). At a later stage of development there are numerous basophil giant cells which appear to be replacing the fibroblasts or to be themselves altered fibroblasts. A few of these basophil cells are multinucleated. Degenerated collagen may be great in amount or scanty. Plasma cells, polynuclears, or lymphocytes are seldom seen. In the more advanced stages there may be a fair number of plasma cells scattered about among the basophil giant cells. There is also an increase in the number of multinucleated cells, and necrotic collagen is represented by small masses here and there (Fig. 5 and 6). Towards the periphery there may be numerous capillaries and much polynuclear cell infiltration. Lymphocytes as a rule are scanty and eosinophils are seldom seen.

Damage to the muscle in the neighbourhood of these rheumatic nodules varies greatly and muscle necrosis is seen only where the nodule cells are infiltrating the connective tissue between the muscle bundles (Fig. 7). Muscle giant cells are rarely found. Elastic tissue fibres within the nodes are widely separated, but seldom is there any break in their continuity.

Tongue. In the anterior and middle third of the tongue there are no nodules, but they are present in the posterior third and become very numerous towards the root. None can be seen in the submucosa. They are more common in the deeper layers lying in the fibrous tissue between the muscle bundles and around the small vessels. They are equally numerous on either side but appear to be more frequent near the mid-line. Damage to muscle is seldom seen to any great extent since the larger expanses of fibrous tissue in this region allow for a considerable spread of the lesion before the muscle tissue is reached (Fig. 8 and 9).

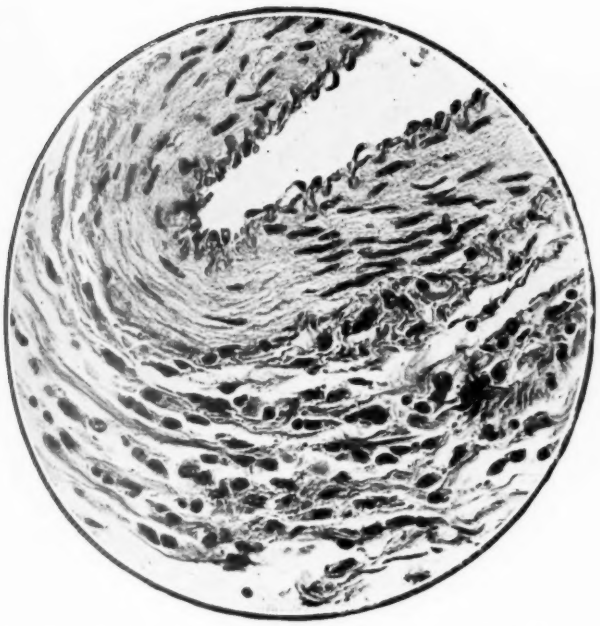

FIG. 1. Case 1. Aschoff nodule in the adventitial tissue of a small artery in the capsule of the tonsil (× 315).

FIG. 2. Case 1. Diffuse rheumatic lesion in the tonsillar capsule (× 90).

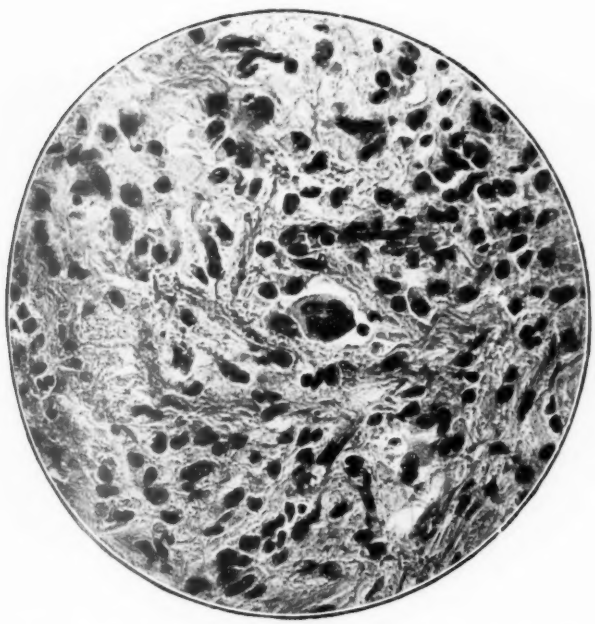

FIG. 3. Case 1. High power view of Fig. 2, showing basophil giant cells (× 315).

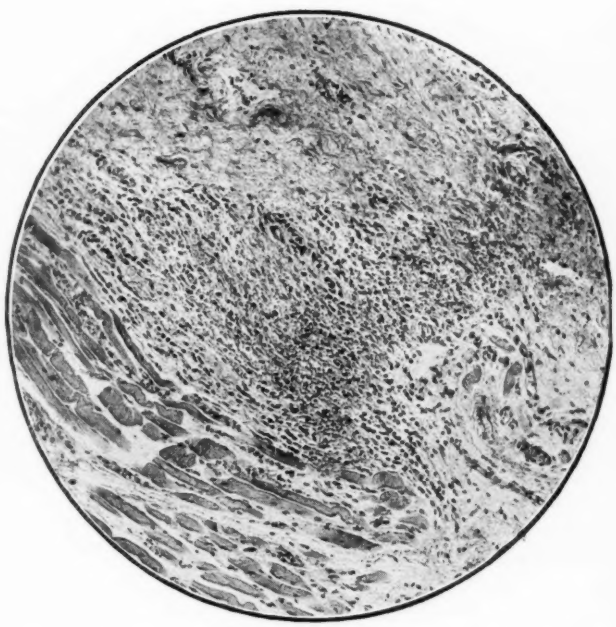

FIG. 4. Case 1. Lesion in the tonsillar capsule compressing the fibres of the superior constrictor muscle. There is marked collagen fibre degeneration (× 90).

FIG. 5. Case 1. Extensive rheumatic lesion in the pharyngeal wall near the œsophagus (× 90).

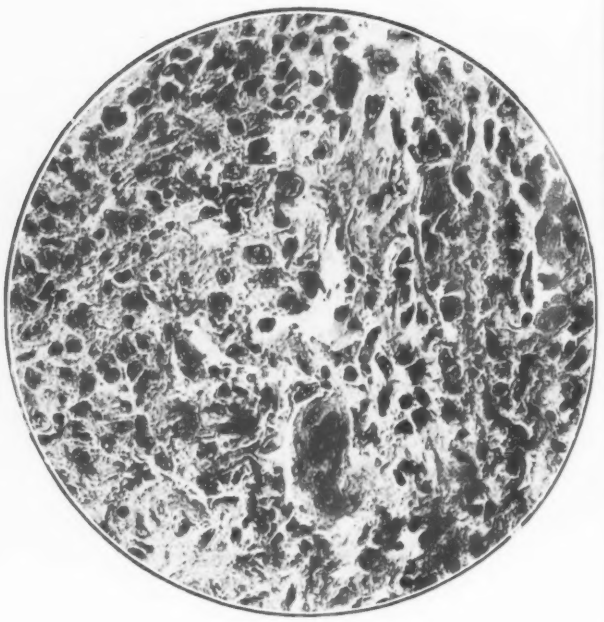

FIG. 6. Case 1. High power view of Fig. 5 to show basophil giant and multinucleated cells and plasma cells (× 315).

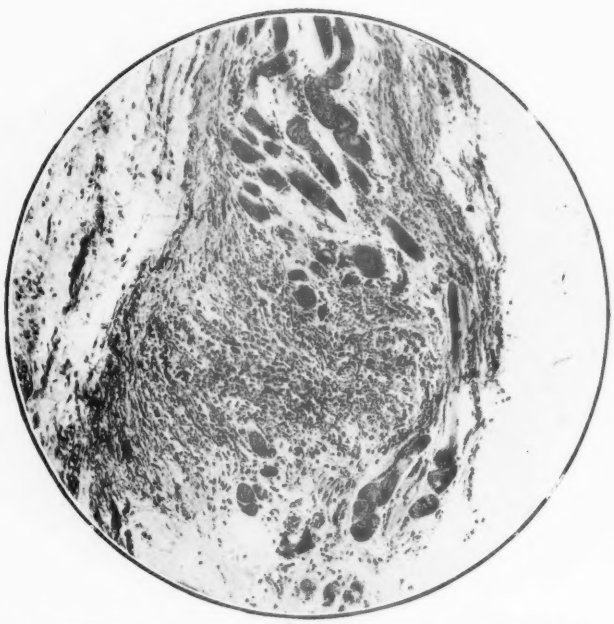

FIG. 7. Case 1. Rheumatic lesion in the wall of the pharynx near œsophageal entrance, showing marked destruction of the muscle tissue (× 90).

FIG. 8. Case 1. Composite rheumatic nodule in the root of the tongue (× 90).

Œsophagus. The upper third only was available for examination. Rheumatic nodules are numerous in the wall of the upper half, but are scanty in the lower part. An occasional one can be seen in the submucosa, but the majority are situated in the muscle connective tissue and peri-œsophageal fascia.

Larynx. There are many nodules in the fibrous tissue around the thyroid cartilage and in the connective tissue of all the intrinsic muscles of the larynx. They are most numerous in the thyro-arytænoid muscles where they are mostly at the advanced stage and have caused much muscle destruction. In the submucosa just above the false vocal cord on either side there are a few small nodules. There are none in the wall of the trachea below the cricoid cartillage, but a few can be seen in the connective tissues between the trachea and the thyroid gland. In all of the regions examined evidence of the existence of previous active lesions is commonly seen in the shape of nodular areas of dense fibrous tissue, sometimes in very close proximity to the active lesions. These scars are very obvious in the constrictor muscles of the pharynx and intrinsic muscles of the larynx.

Lymph nodes. Changes are present in all of the cervical lymph nodes of both sides, but are most conspicuous in the upper deep cervical group. There is no obvious enlargement but the nodes appear swollen. There is very marked proliferation of the endothelial cells and the adenoid tissue is scanty and germ centres are not prominent. Plasma cells are numerous, but eosinophil cells are seldom seen. The sinuses are full of proliferated endothelial cells with a good admixture of polynuclears. Some of the endothelial cells contain two or three nuclei. The fibrous stroma of these nodes is much infiltrated by endothelial, plasma, and polynuclear cells, which are frequently seen in small groups in the vicinity of blood vessels showing intimal proliferation. Specific rheumatic lesions are also present in some of these deep cervical lymph nodes. They are found in the capsule (Fig. 10 and 11) and in the fibrous stroma, particularly in the region of the hilum. In every instance these rheumatic nodules are situated in the connective tissues around the vessels. In the case of the smaller vessels there is sometimes pronounced proliferation of the lining endothelial cells accompanied occasionally by marked destruction of the outer layers of the wall which are within the area of the nodule. The nodules are of the discrete type, corresponding in every way to the typical Aschoff nodule. There is a central area of collagen fibre necrosis surrounded by basophil giant cells—some of which are multinucleated. Some plasma cells may be seen, but polynuclears, lymphocytes, and eosinophils are uncommon. In the fibrous framework of the lymph node the rheumatic nodules are more difficult to demonstrate because of the marked cellular infiltration of the stroma and the close proximity of the lymphoid follicles and crowded sinuses. Where they are situated in the connective tissue surrounding a medium sized vessel however, their true nature can be detected (Fig. 12 and 13). They are then seen to be more cellular than those in the capsule. The basophil giant cells are more numerous and there may be a great many plasma cells. The amount of necrotic collagen present is usually not great.

The above case may therefore be summarized as an example of recurrent rheumatic fever showing rheumatic nodules and scars of previous lesions in the wall of the pharynx, and in the tongue, larynx, and œsophagus. The nodules are particularly numerous in the neighbourhood of the pharyngeal tonsils, the lingual tonsil, and the laryngeal tonsil. A conspicuous number of lesions in their earlier stages of development can be seen in the capsule of both the right and left tonsil. The cervical lymph nodes generally show marked proliferation of the endothelial cells of the sinuses, blood vessels, and reticulum accompanied by much plasma and polynuclear cell infiltration of the stroma. Specific rheumatic lesions are present in some of the upper deep cervical nodes of both sides.

Case 2.—Female, aged 8 years. Admitted as a possible case of miliary tuberculosis. No previous history of rheumatic fever. Died six days after admission.

AUTOPSY PROTOCOL. Moderate hypertrophy and dilatation of the heart. Rheumatic pericarditis, myocarditis, and endocarditis of the mitral and aortic valves. No obvious fibrosis of the valves. Chronic venous congestion of the viscera.

HISTOLOGICAL EXAMINATION (Figures 14 and 15). The tonsils are much enlarged. The crypts are not dilated but contain many pus cells and gram-positive cocci. Frequently these pus cells and cocci extend into the subepithelial tissue, the epithelial layer having been ulcerated. Sometimes in these ulcerated spots there may be many plasma cells. Throughout the adenoid tissue plasma cells are numerous, but eosinophils are not seen. There are also areas where endothelial cell proliferation is marked but this is not a very prominent feature. There are numerous rheumatic nodules in the tonsillar capsule on both sides, and in the connective tissue of the superior constrictor muscles at the base of the tonsils they are even more numerous (Fig. 14 and 15). In the pharyngeal wall outside of this region there are no nodules. The tongue, larynx, and upper part of the œsophagus are likewise free from lesions.

Lymph nodes. Those of the upper deep cervical group which were the only ones examined show marked proliferation of the lymphoid cells and germ centres are small and not easily seen. Plasma cells are numerous but there is no evidence of increased proliferation of the endothelial cells. The small blood vessels appear normal and there are no specific rheumatic nodules.

In Case 2, an example of rheumatic fever with a history of recent onset, there are found specific nodules in the capsule and the muscle bed of the right and left tonsil. The regional lymph nodes show a marked proliferation of the lymphoid cells, but there are no other conspicuous changes.

Case 3.—Female, aged 8 years. Admitted with joint pains and heart disease. History of rheumatism since the age of four. The chief complaint has always been of pain in the muscles and joints of the arms and legs, but in the last six months there have been frequent attacks of severe abdominal pain. No history of throat trouble. There is a brother of six with rheumatic heart disease. Death took place six weeks after admission.

AUTOPSY PROTOCOL. Hypertrophy and dilatation of the heart, with marked fatty degeneration of the myocardium. Rheumatic pericarditis, myocarditis, and endocarditis of the mitral, tricuspid and aortic valves. A fair amount of yellow fluid in the peritoneal and pleural cavities. Chronic venous congestion of viscera. Moderate fibrosis of all valve leaflets.

Case 4.—Female, aged 7 years. Admitted with pericarditis. The illness began with pain in the muscles and joints fourteen days previously. Died five days after admission.

AUTOPSY PROTOCOL. Slight hypertrophy and dilatation of the heart with rheumatic pericarditis, myocarditis, and endocarditis of the mitral and aortic valves. No obvious fibrosis of the valve leaflets. Chronic venous congestion of viscera.

HISTOLOGICAL EXAMINATION (Cases 3 and 4; Figures 16 and 17). Cases 3 and 4 show similar changes. The tonsils are only moderately hypertrophied and they show the same histological features as Case 2. There are a few rheumatic nodules in the tonsil capsule with a still fewer number in the tonsillar bed tissues (Fig. 16 and 17). In each case the picture is the same on both sides. The rheumatic lesions are all at an early stage of their evolution and there is practically no destruction of muscle. There are no lesions in the rest of the pharyngeal wall, nor in the tongue, larynx, or upper part of the œsophagus.

Lymph nodes. In both cases the upper deep cervical group of lymph nodes show the same lymphoid cell hyperplasia observed in those of Case 2.

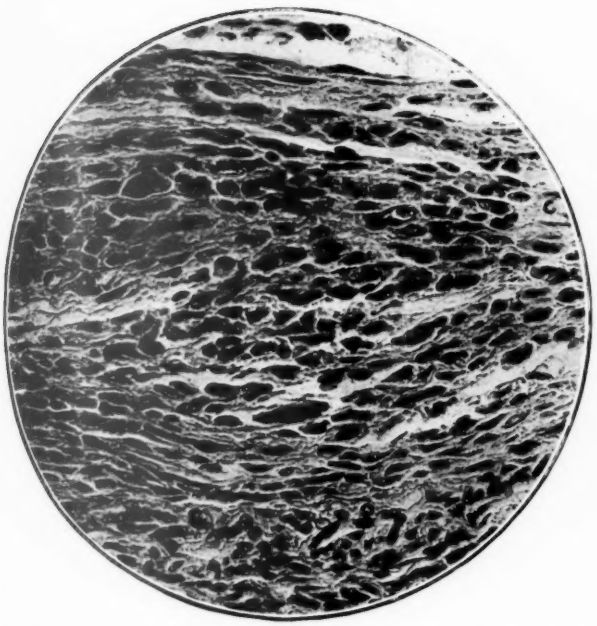

FIG. 9. Case 1. High power view of an area in Fig. 8 (× 315).

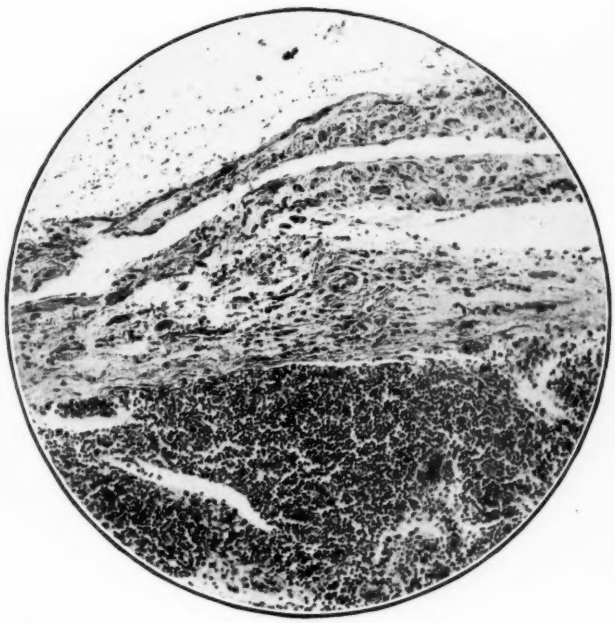

FIG. 10. Case 1. Rheumatic lesion surrounding a small vessel in the capsule of a regional lymph node (× 90).

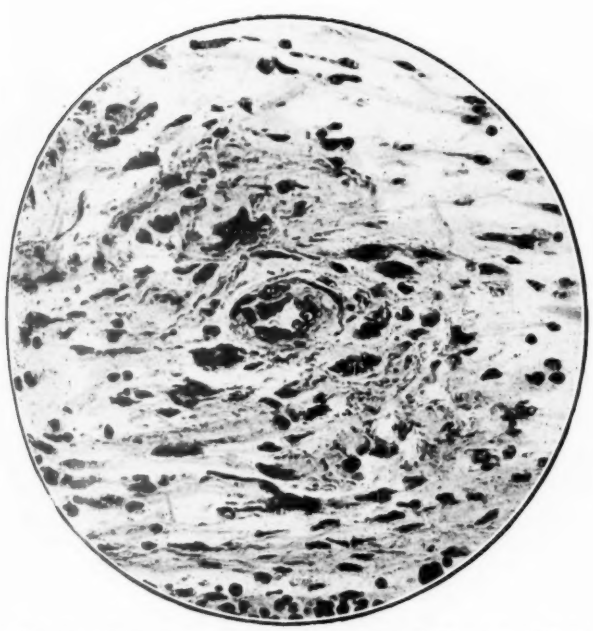

FIG. 11. Case 1. High power view of Fig. 10. Note the collagen necrosis, the basophil giant and multinucleated cells and the proliferation of the vascular endothelium. Part of the vessel wall is necrotic (× 315).

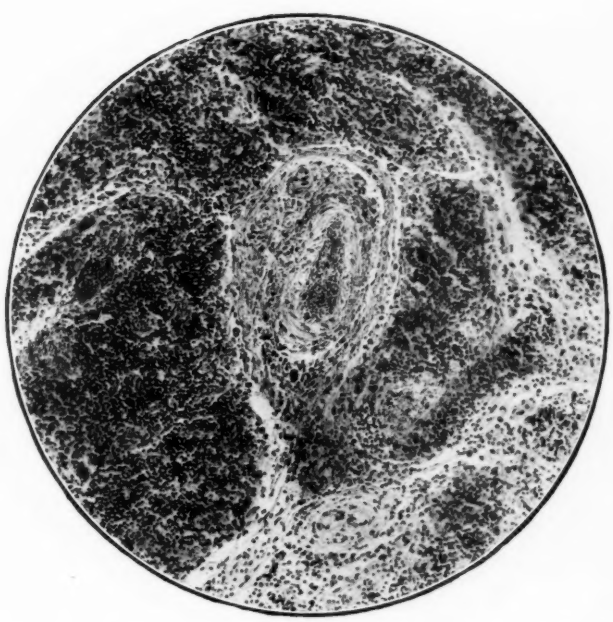

FIG. 12. Case 1. Rheumatic nodule in the neighbourhood of a small vessel in the fibrous stroma of a deep cervical lymph node (× 90).

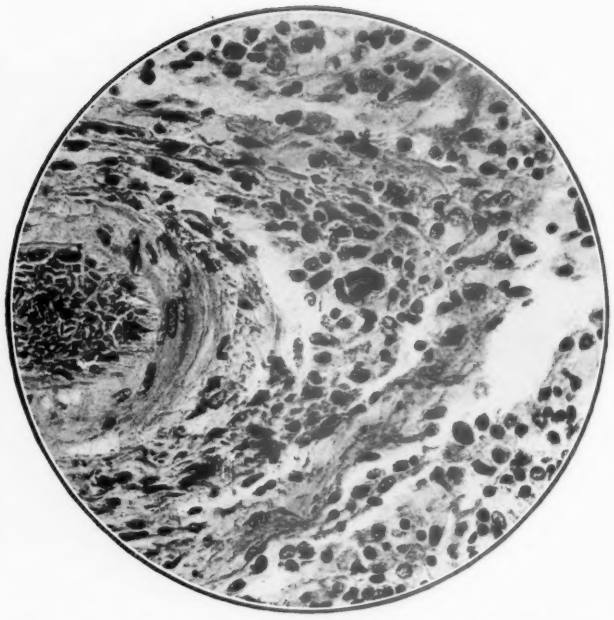

FIG. 13. Case 1. High power view of Fig. 12, showing basophil giant and multinucleated cells and plasma cells. The amount of collagen degeneration is slight (× 315).

FIG. 14. Case 2. Section through the bed of the tonsil to show the nodules in the connective tissue of the muscle (× 90).

FIG. 15. Case 2. High power view of one of the nodules in Fig. 14, showing collagen degeneration and proliferation of fibroblasts (× 315).

FIG. 16. Case 3. Section through the base and muscle bed of the tonsil, showing rheumatic lesions of the capsule and muscle connective tissue (× 90).

Cases 3 and 4 are both examples of rheumatic infection, one a recurrent case and the other of recent duration. Both show early stage rheumatic nodules in the tonsil capsules and in the immediately surrounding tissues of the tonsillar bed. There is marked lymphoid cell hyperplasia in the upper deep group of cervical lymph nodes, but no rheumatic nodules can be seen.

Discussion.

The pharyngeal lesions described above provide a specific histological basis for the sore throat so frequently associated with rheumatic infection. Their symmetrical distribution round the adenoid tissue of the throat suggests

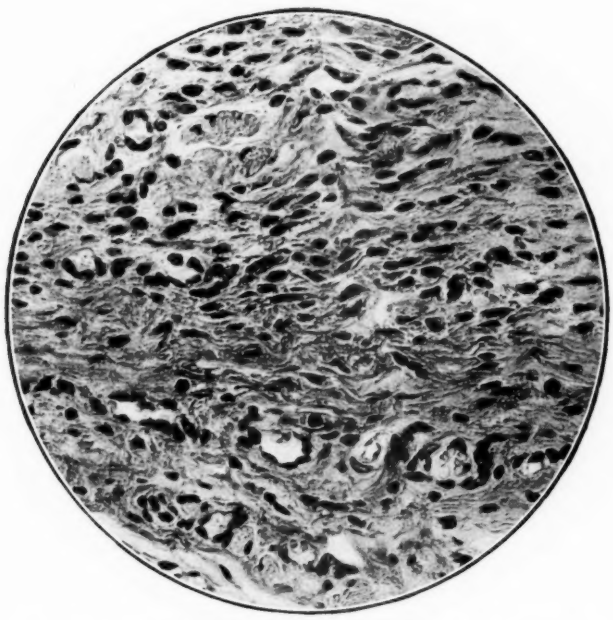

FIG. 17. Case 3. High power view of the capsular lesion in Fig. 16, showing degeneration of collagen and basophil fibroblastic proliferation (× 315).

that the tonsils, and less frequently the other adenoid collections, are the portal of entry of the infection. That there may be no clinical evidence of the presence of such lesions round the tonsils is shown by the three cases with no symptoms or complaint of throat trouble.

The first case throws considerable light on Schlesinger's[5] clinical observation in regard to the association between sore throat and recurrence of rheumatic fever symptoms. Schlesinger has shown that in convalescent rheumatic cases a definite time interval, approximately 10 to 21 days, intervenes between the onset of a throat infection and the reappearance of rheumatic symptoms. The pathogenesis of Schlesinger's clinical picture is well represented by the histological findings in Case 1. Here we have a recrudescence of acute rheumatic symptoms 14 days or so after a severe

throat attack. There are rheumatic lesions in the neighbourhood of the tonsils and also of the other adenoid tissues of the throat. A generalized simple cervical adenitis is present and there are rheumatic nodules in some of the lymph nodes in the upper deep cervical groups.

The presence of the Aschoff nodules in the lymph nodes draining areas where there are extensive rheumatic lesions is evidence of a specific virus spreading via the lymph stream.

Summary.

Rheumatic nodules have been found in the pharyngeal tissues of two recurrent and two early cases of rheumatic fever. The nodules were more commonly seen in the neighbourhood of the tonsils, radiating out from the tonsillar capsule into the connective tissue of the muscles of the pharynx.

Similar lesions were present in the region of the lingual and laryngeal tonsils in one of the recurrent cases. In this case also there were significant changes in the regional lymph nodes. These changes consisted of marked endothelial hyperplasia with much polynuclear and plasma cell infiltration.

Aschoff nodules were found in the connective tissue surrounding the vessels in the capsule and fibrous stroma of some of the nodes in the upper deep cervical group on both sides.

I have to thank my colleagues on the Staff of the Bristol Royal Infirmary for their kindness in allowing me access to the clinical notes of their cases.

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CHRONIC INTUSSUSCEPTION IN CHILDREN

BY

D. M. SUTHERLAND, M.D., F.R.C.S.

(From the Royal Children's Hospital, Manchester.)

Chronic intussusception in children is of relatively uncommon occurrence, and the reported cases show that its symptoms are very variable. Usually a tumour is present and the condition is often ascribed to tuberculous mesenteric glands or to tuberculous peritonitis. The ascites produced by tuberculous peritonitis was simulated in a case of chronic intussusception described by Spencer[1]. The symptoms of the condition in all the reported cases certainly differ markedly from those of acute intussusception, with its classical signs of acute intestinal obstruction and the passage of blood and mucus per rectum. The rarity of the condition and the information which the history of the case gives in diagnosis supply the reasons for the publication of the following case.

Case report.

A boy (A. B.), aged three years, was admitted to the Royal Manchester Children's Hospital in April, 1932, suffering from acute abdominal pain referred to the region of the umbilicus. The parents stated that the child had suffered from obstinate constipation for at least two months and that the bowels had previously acted regularly without the aid of purgatives: he had also lost much weight. During this time they noticed that he had periodical attacks of colicky pain, which caused him to stop playing; he would often lean over a chair for a few minutes until the pain disappeared. The attacks became more frequent and the day before his admission into hospital they occurred almost hourly and caused him to scream. He had also had frequency of micturition, but had vomited once only.

On admission to hospital a tumour was palpable in the right iliac fossa. The mass was hard but not tender. The temperature was normal. The mass was slightly movable; there was no rigidity or evidence of visible peristalsis and the respiratory abdominal movements were normal. There was no history of the passage of blood or mucus per rectum. The initial diagnosis was that of tuberculous mesenteric glands, and it was decided to keep the child under observation. For the following seven days there were repeated attacks of pain of a severe type referred to the penis and suprapubic region; the pain often disappeared with micturition and the condition simulated that due to a vesical calculus. The bowels acted every day with the aid of aperients; there were no signs of blood or mucus in the stools, nor of visible peristalsis. There was no vomiting.

On account of the recurrent attacks of pain and the persistence of the tumour in the right iliac fossa, a laparotomy was performed seven days after admission to hospital. A chonic intussusception was found. The terminal half-inch of the ileum had prolapsed through the ileo-caecal valve and the two were invaginated for about four inches into the ascending colon, forming an ileo-colic intussusception.

There was a mass of enlarged ileo-cæcal glands with a mobile cæcum, but no mesentery to the ascending colon. The intussusception was reduced and the bowel found to be healthy. The appendix was removed and examined microscopically; it showed no evidence of tuberculous infection.

Discussion.

The outstanding features of this case, during its period of observation in hospital, were the intermittent attacks of pain referred to the penis and umbilicus. Waugh[2] has described three cases of acute intussusception with referred penile pain, in which the ascending colon had an abnormal mesentery. He attributed the pain either to the direct pull of the abnormal meso-colon with the extra weight of an intussusception on the kidney, or to the meso-colon dragging on the kidney, thus rendering it mobile and causing traction on its nerves. He suggested that this referred pain could be used to recognize the existence of an abnormal mesentery. In the present case there was no abnormal mesentery, and the tumour due to the intussusception could only be brought to the surface of the incision with difficulty.

The character of the pain was, however, exactly that described by Waugh, and it was thought at one time that the child must have a vesical calculus. The features in the case which seemed to differentiate the diagnosis from tuberculosis were the frequency and the severity of the attacks of pain. The mass in the right iliac fossa could easily have been mistaken for ileo-cæcal tuberculosis, but in this condition and in other types of abdominal tuberculosis in children, the attacks of pain are not often so severe or so persistently recurrent as in the present case.

The histories of this and of previously reported cases show that the passage of blood and mucus per rectum, and the signs of acute intestinal obstruction are often absent in cases of chronic intussusception. Symptoms of chronic obstruction were undoubtedly present as action of the bowels was only effected by the means of purgatives.

Another feature of the present case was the wasting, which, combined with the presence of an ileo-cæcal tumour, suggested the diagnosis of tuberculosis.

Summary.

A case of chronic intussusception of the ileo-colic type in a child is reported. In it the most salient feature consisted of severe and recurrent attacks of colic in which the pain was referred to the penis and supra-pubic region. Symptoms of chronic intestinal obstruction and wasting were present, but at no time was blood and mucus passed per rectum.

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A CASE OF DWARFISM AND CALCINOSIS

associated with WIDESPREAD ARTERIAL DEGENERATION

BY

REGINALD LIGHTWOOD, M.D., M.R.C.P., D.P.H.

(From The Hospital for Sick Children, Great Ormond Street, London.)

In 1931 there was admitted to Dr. Robert Hutchison's ward at The Hospital for Sick Children, Great Ormond Street, a dwarfed child of 2 years and 3 months. The colour of her skin was yellow like a faded leaf. The urine was albuminous and the blood pressure high. The peripheral arteries were hard and tortuous. Roentgenograms showed irregular, transverse bands of osteosclerosis and osteoporosis in the metaphyses of certain of the long bones, excessive calcification of the skull, and calcification of the larger peripheral arteries. At first it was thought that the case was unique, but medical literature showed it to be not without parallel. An autopsy provided an opportunity for histological study which, together with the clinical and post mortem findings, forms the basis of this report.

Widespread calcification in infancy and childhood is a rare but not unknown phenomenon. Bryant and Hale White[1] reported the case of a male infant, fatal at the age of 7 months, in whom the necropsy showed a calcifying endarteritis obliterans and calcification in the endocardium, associated with great congenital dilatation of the urinary tract. We must regard this association of congenital dilatation of the urinary tract and extreme arterial disease as unusual and probably fortuitious. Thus there is no mention of degeneration in the arteries in Holt's[2] account of his eight cases of congenital hydronephrosis with dilatation of the ureters, nor is there in those reported by Poynton and Sheldon[3]. And in an extensive experience of cases of congenital dilatation of the urinary tract studied at the Hospital for Sick Children, though the state of the arteries has not been made the subject of special study, no instance of arterial degeneration or thickening has been catalogued among them. Indeed, the systolic pressure was not very high in any, though it was raised as a rule in the older cases, especially when renal insufficiency had made its appearance. The findings in five of these cases are summarized in Table 1. Five children with congenital hydronephrosis, investigated by Neale[4], Table 2, suggest also that the blood pressure rises with the onset of renal failure, and once again no evidence of arterial degeneration is recorded. From our own experience and from a study of the literature, it would seem reasonable to take the view that extreme arterial degeneration, and particularly calcification, are

not the end-results of the renal failure due to congenital dilatation of the renal tract. In the case of Bryant and Hale White the authors themselves did not think that the arterial calcification could be explained as the result of the renal abnormality.

TABLE 1.

CASES OF CONGENITAL DILATATION OF RENAL TRACT.

(The Hospital for Sick Children.)

Age.	Sex.	Anatomical defect.	Blood urea. Mgrm. %	Blood pressure.
6	Male ...	Urethral obstruction ...	114	135 syst.
13	Female ...	Urethral obstruction ...	128	130 syst.
6½	Female ...	Dilatation of ureters ...	42	115 syst.
2	Male ...	Urethral obstruction ...	109	90-95 syst.
4	Female ...	Urethral obstruction ...	312-427	140 syst. 85 diast.

TABLE 2.

CASES OF CONGENITAL HYDRONEPHROSIS.

(Dr. A. V. Neale.)

Age.	Renal failure.	Blood urea. Mgrm. %	Blood pressure.
7½	Absent	24·8	100/80
6½	Absent	30	110/90
14	Present	56	110/85
7¾	Absent	39	110/90
8	Present	78	130/95

Arteriosclerosis, as seen in the adult, is known in children but usually occurs only at the end of childhood and many of the cases have been renal dwarfs. Thus of four cases of arteriosclerosis, described by Evans[5], one was nine years old and three were fourteen. From his histological examinations he argued that the vascular lesion was identical with that found in the diffuse hyperplastic sclerosis of adults, and he considered it to be an active inflammatory lesion completing the link between arteriosclerosis and the endarteritis seen in the lesions of tuberculosis and syphilis. Calcification did not occur in his cases.

Hodgson[6] in his ' Treatise on Diseases of the Arteries ' (1815), says his friend Young ' possesses a temporal artery which he removed from an infant 18 months old, in which the coats of the vessel were covered with a complete tube of calcareous matter.' That severe arterial hyperplastic sclerosis may

be fatal in childhood is shown by a case of general systemic and pulmonary arteriosclerosis recorded by Hawkins[7]. Microscopically there was development of fibro-cellular tissue in the intima but no degeneration or calcification. Death resulted at 11 years from thrombosis of the renal arteries.

Primary arterial hypertension has been recorded in the young though it is rare. Cases have been described by Amberg[8], Faerber[9], Hutchison and Moncrieff[10], Craig[11], and others. The state of the arteries in many of the cases has not been ascertained, there being no post mortem verification. In the case of Hutchison and Moncrieff[10], the latter compared histological sections from their case with controls taken from a child of the same age and no trace of difference was found. Craig[11] verified that there was hypertrophy of the tunica media in the coronary, renal and cœliac arteries of his case, together with atheroma of the aorta, and ischæmic atrophies in the kidneys; but no calcification had occurred.

In our case, and in that of Bryant and Hale White, while the brunt of the changes fell on the arteries, pathological calcification occurred also in other tissues: in the endocardium in theirs and, as will be described later, in the kidney, lung, dura mater, endocardium and peritoneum in ours. In consequence there arises the possibility that the disorder is one in which calcium and phosphorus metabolism is disturbed. During the last few years much has been written on hypervitaminosis-D in which widespread calcareous deposits may occur.

By the administration of irradiated ergosterol to rats in excessive doses a condition described as hypervitaminosis has been produced. In general the results [12, 13] in animals are anorexia, wasting, diarrhœa and death. There is hypercalcæmia, an increase in the inorganic blood phosphate, and an increased urinary excretion of calcium. Variations in calcium and phosphorus intake modify the effects. Post mortem, calcium salts are found deposited in the tissues especially in the kidneys, myocardium and walls of the large arteries. The thymus and spleen are atrophied and the bones may show hypercalcification or they may in time become demineralized[14].

Moreover, it would appear from the details of the case recorded by Putschar[15] that hypervitaminosis is a disease not only of laboratory animals. This was an infant who became weak soon after birth, with vomiting, a certain rigidity of the skin, and a sub-febrile temperature. Though there were no manifestations of rickets six drops of irradiated ergosterol (Vigantol) were given daily and continued for ninety-six days. After seventy days of this treatment leucocytes and albumin were found in the urine. Death occurred at $5\frac{1}{2}$ months and at the autopsy Putschar found calcification in both cortex and medulla of the kidneys. We cannot accept without question that these changes were necessarily produced by the treatment, because our case and that of Bryant and Hale White did not receive any food or drug in the least likely to contain vitamin-D in more than physiological quantities. We cannot go further than to say that though Putschar's case was probably an instance of hypervitaminosis-D, it might possibly be of a nature similar

to the one we are describing, in which careful inquiry showed that no vitamin-D preparation had been given in excessive quantity.

Another clinical instance of hypervitaminosis-D, fatal at 18 months, has been described by Thatcher[16]. The symptoms were weakness and anorexia. Although there was no rickets the infant had received about twice the recommended dose of irradiated ergosterol, from the age of 13 months until a few days before death. Autopsy showed deposits of calcium throughout the renal medulla. The appearances suggested that the deposits were formed as casts within the tubules. Calcareous masses had obstructed and caused dilatation of some tubules. The blood vessels were healthy and no calcification had occurred apart from the kidney. Thus the changes were not so extensive as in Putschar's case and as in experimental hyper-vitaminosis-D.

Calcinosis has been recorded by Kennedy[17] in a well nourished child of 6 years. Difficulty in walking was the earliest symptom of her complaint, and hysteria had been diagnosed until hard, bone-like masses appeared in the flexures. For three years she received a ketogenic diet and during this time the calcium deposits were gradually absorbed. No suggestions as to the cause of her disease were advanced.

Cramer[18], working with rats on synthetic diets in which the proportion of inorganic salts in the salt mixture was varied so as to produce mineral imbalance, has found that the omission of magnesium salts, the ions of which are biologically antagonistic to calcium ions, produced extensive degenerative lesions in the glomeruli and tubules of the kidneys. Sometimes but not always, these changes were accompanied by calcareous deposits. The significance of this observation lies in the fact that it appears possible to produce experimentally such changes by dietetic measures not involving the introduction of toxic substances. Cramer suggests that the mineral imbalance may have had a specific effect on the renal tubules and glomeruli. His experiments, which are not yet concluded, are giving somewhat different results from those of Kruse, Orent and McCallum[19], who used diets carefully purified so as to contain about 40 times less magnesium than did those of Cramer, and produced much more general pathological lesions.

Case report.

HISTORY.—A female infant, aged 2 years 3 months, was admitted to the hospital because she had never grown properly. She had been seen twice by a specialist, congenital heart disease being suspected. Vomiting had occurred from time to time. At 5 months old she was in hospital on account of facial paralysis which appeared when she was teething. Except for an attack of diarrhœa there had been no other illnesses. At 15 months she was a tiny little creature, 17½ inches long, and weighing 12-13 lbs; there was a cardiac murmur loudest at the base. During the last 12 months she had gained no weight. There seemed to be difficulty in swallowing, and much flatulence causing pain and crying. Though she could move all her limbs she had never walked.

FEEDING.—For the first five weeks she was breast fed and then "Allenbury's" foods were used until she was 8 months old, when the attack of diarrhœa, to which allusion has been made, was treated by giving a mixture of equal parts of milk and lime water for six weeks. Subsequently the diet followed was not abnormal except

that one teaspoonful of lime water was given in each feed until she was one year old. Between 15 and 18 months half an eggspoonful of Scott's emulsion was given daily and for a short period of a fortnight before admission she was receiving Ostelin mii daily.

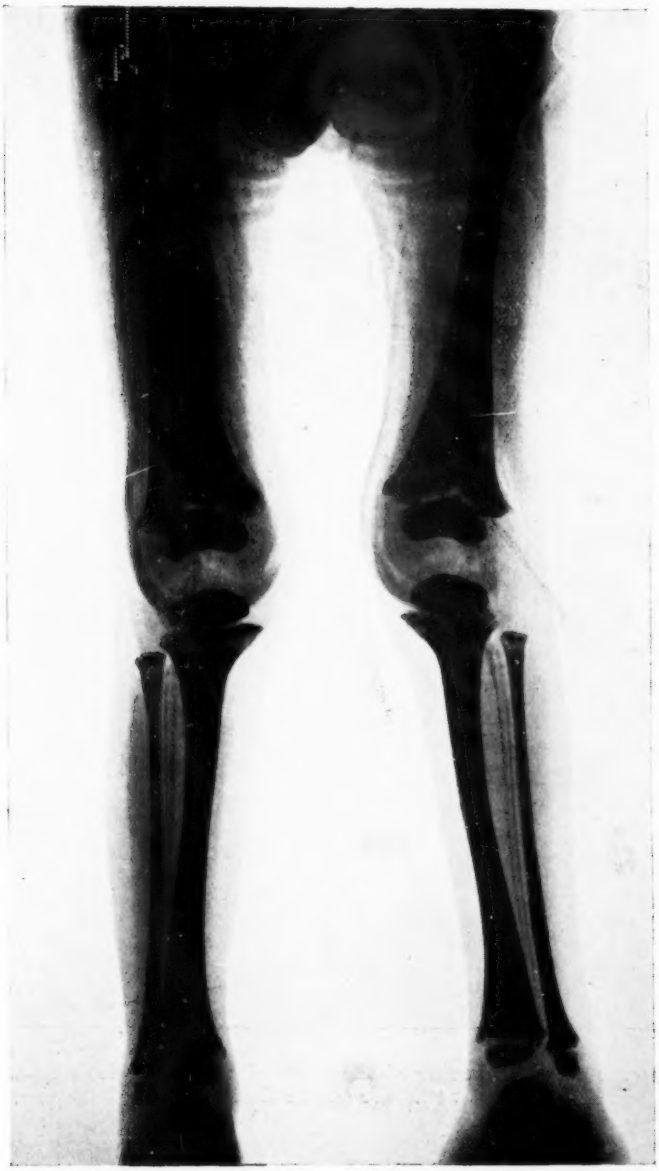


FIG. 1. There is osteosclerosis of the shafts and irregularity of the epiphyseal lines. In the metaphyses alternating zones of osteosclerosis and osteosporosis are to be seen. The femoral, popliteal and posterior tibial arteries are visible on account of the calcium deposited in their coats.

FAMILY HISTORY.—The parents were healthy and well-to-do, there was no consanguinity. No miscarriages had occurred and the mother had not taken cod-liver oil, ostelin, radiostol or any preparation of lime during her pregnancy. The

family tree was traced back for four generations on the father's side and three generations on the mother's. The paternal grand-mother had died at 56 of cerebral hæmorrhage, and the paternal great grand-father as an old man of renal disease. On the mother's side a grand aunt had died of nephritis at 29. Otherwise there was no family history of renal or vascular disease, or of any other condition bearing on the case.

EXAMINATION.—On examination she was found to be a dwarf with a biscuit-coloured skin. Her apparent age was 10-12 months and her mentality corresponded with this. Her nutrition was poor, she had a moderate knock-knee but no beading of the ribs. All the teeth had erupted but were carious. Heart: No enlargement was detected and there were no murmurs. The second sound over the base was accentuated. Systolic blood pressure 180 mm. Lungs: normal. Vessels: Radial

FIG. 2. There is much thickening of the vault of the skull with osteosclerotic changes at the base and in the maxillæ.

pulse hardly perceptible, but the radial artery could be felt as a hard and tortuous cord. The brachial and femoral arteries were hard and easily felt. All these arteries could be seen in the roentgenograms (Fig. 1). The retinal arteries were narrow and had a double contour. Central nervous system: A left external rectus and a right facial paresis were found. Abdomen: The liver, spleen and kidneys were not felt, and the bladder, though palpable, was not distended.

INVESTIGATIONS.—The urine was acid and contained a considerable amount of albumen, a few red and white corpuscles, and a few hyaline casts. The Wassermann reaction was negative. Blood urea 169 mgm. per 100 c.c. A urea concentration test was carried out, 3 grammes of urea being used: in the first hour the urea concentration in the urine was 1·45 per cent., in the second 1·50 per cent. These findings are

indicative of renal insufficiency. Blood cholesterol 196 mgm. per 100 c.c. (normal 100-200). Serum calcium 11 mgm. per cent. (normal 9-11 mgm. per cent.). Blood phosphorus 6·68 mgm. per cent. (normal 4-5·5 mgm. per cent.).

After admission to hospital she was found to have slight irregular pyrexia and she vomited occasionally. A few days later the temperature rose to 102° and she died somewhat unexpectedly.

AUTOPSY.—The body was that of a stunted, marasmic infant with a yellowish skin.

The skull was considerably thickened throughout, and the tentorium cerebri heavily calcified; the dura mater, especially at the base, showed some irregular calcification (Fig. 2). The substance of the brain was normal but the cerebral arteries were somewhat prominent.

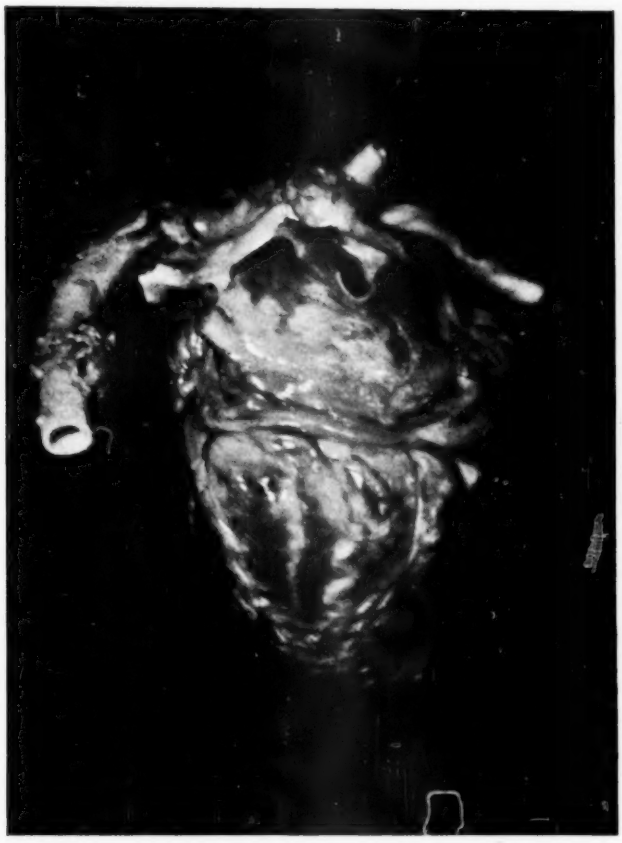


FIG. 3. The heart, and especially the ventricles are moderately enlarged, and the coronary arteries present a unique appearance of tortuosity and thickening.

The heart, and especially the ventricles, were moderately enlarged, and the coronary arteries presented a unique appearance of tortuosity and thickening (Fig. 3). On the outer surface of the auricular appendix, and in the endocardium of the auricles and ventricles, small patches of calcification were seen.

The state of the vessels was made the subject of careful study. Macroscopically nothing abnormal was noted in the veins, but under the microscope certain of them showed a slight thickening of the tunica adventitia. The capillaries showed no structural alterations. The arterial system was extensively diseased.

The aorta and the pulmonary artery, with their valves, were normal to the naked eye and even histologically the aorta showed no change. The largest of the arteries also appeared normal, but elsewhere, throughout the arterial system, there were proliferative and degenerative changes with the deposition of much calcium. Generally speaking, the medium-sized and small arteries were the most affected. Thus the pulmonary stem was normal but the pulmonary branches were atheromatous, the aorta showed no change until the iliac arteries were reached, and the arteries of the limbs were atheromatous. In the thorax it was seen that atheroma had affected the intercostal arteries but the subclavian vessels had escaped. In the neck the carotids appeared normal and the circle of Willis showed only minute histological changes, to be described later. The axillary arteries were normal but the brachials were atheromatous. The branches of the abdominal aorta showed degeneration seen well, for example, in the left colic branch of the inferior mesentric vessel.

HISTOLOGY OF ARTERIES.—The exact nature of the changes found in these arteries raises points of considerable difficulty, but their main histological features can be

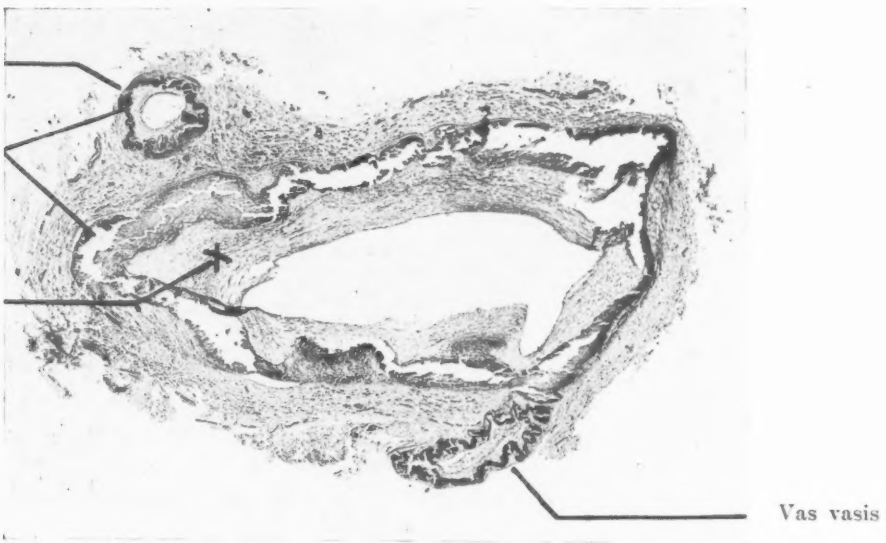


FIG. 4. A low power microphotograph (X 20) of the femoral artery. The sub-intima has proliferated and subsequently degenerated and slight calcification appears to have occurred in it. The media is partly destroyed and largely calcified (the calcium shows black). The adventitia is fibrosed. The vasa vasorum (top left and bottom right) show similar changes.

made clear with the aid of some representative microphotographs. A section of the femoral artery may be taken to illustrate the changes seen in a vessel of intermediate size. An enormous fibro-cellular and concentric proliferation, of what appears to be sub-intimal connective tissue, has taken place and degenerative changes have followed in it. A feature of this degeneration is the laying down of fine deposits of calcium. Furthermore, the internal elastic lamina has disappeared and the tunica media has undergone widespread destruction and massive calcification. The white fibrous tissue of the tunica adventitia shows some increase. Essentially similar changes are to be seen on a smaller scale in the vasa vasorum (Fig. 4). This sub-intimal proliferation would remind one of arteriosclerosis if it were less in amount and less concentrically distributed; the medial changes cannot fail to bring Mönckeberg's degeneration to mind. Figure 5 illustrates the changes seen in a

smaller vessels under a higher magnification. The microphotograph shows a small branch of the left coronary artery. The same sub-intimal proliferation is seen, the same disappearance of the internal elastic lamina, and the same calcification in the tunica media. Every branch of the coronary arteries showed similar or even greater change. The heart muscle shown in Figure 5 is normal but in other fields this also showed areas of degeneration and calcification, presumably a result of coronary occlusion. Thus it is highly probable that had this child been old enough to detail her symptoms, cardiac and possibly anginal pains would have been described, and it is interesting to speculate if the pain already mentioned in her history had any such significance.

It has been mentioned that the largest vessels (aorta, pulmonary, subclavian, axillary, carotid and renal arteries) were normal and it was a matter of interest to look for the exact point where the earliest changes would make their appearance.

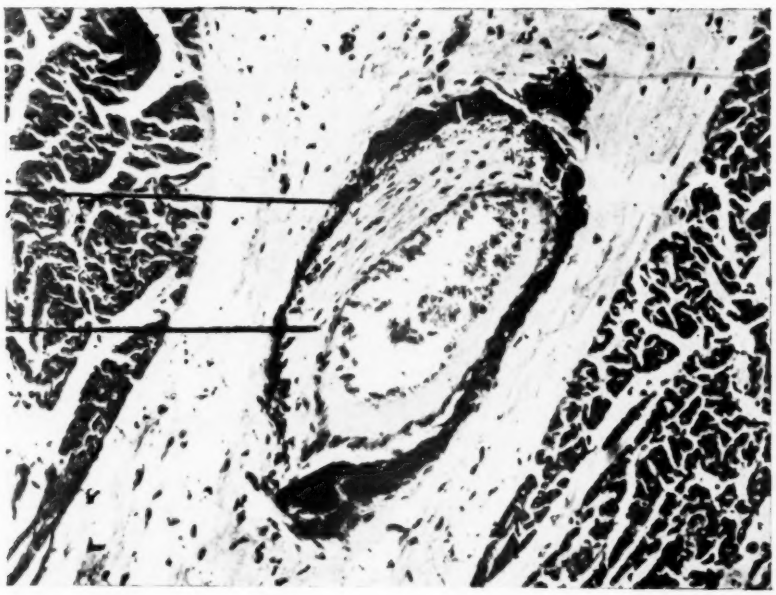


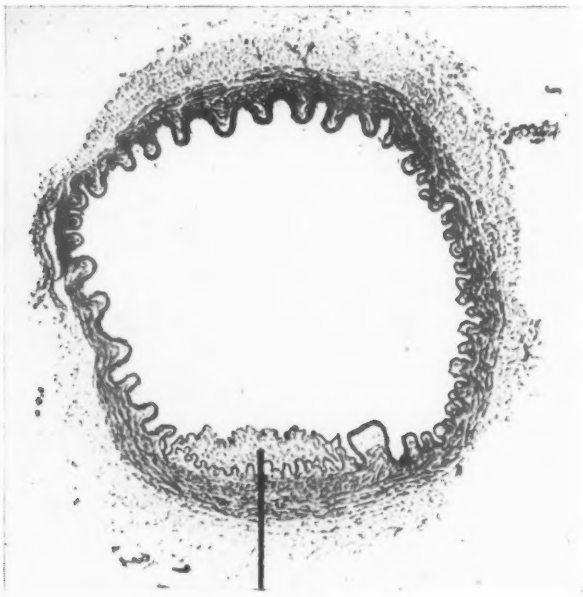
FIG. 5. A high power microphotograph (X 200) of a branch of a coronary artery. The sub-intimal layer has proliferated and degenerated, the media is calcified (calcium shows black). Many other coronary branches show an even greater degree of endarterial obliteration than is seen here.

By good fortune a microscopical section of a portion of the circle of Willis provided this opportunity. Here the whole extent of the internal elastic lamina was seen to be thickened and at one point it was split to enclose a patch of proliferating fibroblasts (Fig. 6). Strongly suggesting an origin primarily vascular, this localized proliferation must be taken as highly significant. No changes were to be seen in the medial or adventitial coats of this vessel and no calcification. In the middle cerebral artery there was thickening of the internal elastic lamina but no degeneration, and the tunica adventitia showed slight increase.

There were patches of calcification in the trachea. The branches of the pulmonary artery were so thick and rigid that they stood out from the lung. There was a terminal, confluent bronchopneumonia and œdema of the lower lobes. Histologically the parenchyma of the lung showed much degeneration and scattered calcification. In the parietal pleura covering each rib posteriorly, there was

thickening and deposition of calcium. There were patches of thickening, apparently with the deposition of calcium, in the peritoneum covering the stomach. There were slight fatty changes in the liver, and the spleen showed in moderate degree the changes associated with a terminal septicœmic condition.

The kidneys were small, tough and pale. The capsule was adherent, and the cortex narrow, with loss of differentiation between it and the medulla. The arteries were thickened and gaping, and in the region of the hilum they were seen to be calcified. The main renal arteries appeared normal except for the presence of an accessory left renal artery going to the lower pole: a not uncommon finding which had resulted in no disturbance.



Fibroplastic proliferation splitting the internal elastic lamina.

FIG. 6. A low power microphotograph (X 75) of a portion of the circle of Willis which illustrates the earliest apparent arterial change. Cellular proliferation is seen under the intima at 6 o'clock. An elastic tissue stain shows that this proliferation has split the internal elastic lamina. Note the thickening of the internal elastic lamina elsewhere.

HISTOLOGY OF KIDNEYS.—The histological appearances in the kidneys are difficult to describe and difficult to interpret. Of all the small arteries examined the renal arterioles most nearly approached the normal, and degenerative changes were conspicuous by their absence. In most of them some hypertrophy of the muscular coat was present, though this point required to be established by comparisons with control material. The vessel pictured in Figure 7 shows a little fibrosis of its tunica adventitia and a moderate medial hypertrophy; the intima is normal, and the internal elastic lamina can be recognized by appropriate staining. The renal parenchyma showed a remarkable degree of interstitial fibrosis (Fig. 8). A majority of the glomeruli were pathological: either fibrosis of the tuft, or of Bowman's capsule, or of both. Sometimes this fibrosis was slight, sometimes the

changes had proceeded to hyalinization. Many of the glomerular tufts showed a small deposit of calcium eccentrically placed (Fig. 9), a few were solid with calcium, and sometimes a fibrosed Bowman's capsule contained a calcium deposit. The renal tubules also showed a great variety of pathological change: some normal, some dilated and some fibrosed. Both secreting and collecting tubules were the frequent site of calcium deposition. An exhaustive study of hundreds of tubules left little room for doubting that the calcium had usually precipitated as a cast within the tubule. Sometimes the calcium cast contained the remnants of dead cells and sometimes the tubular epithelium itself was encrusted with a thin layer of the mineral. Often calcification within a tubule had proceeded to widespread tissue destruction in its vicinity, thus giving rise to large deposits. The dilatation of tubules might be explained either as a result of the fibrosis, or blockage by these deposits. Visible calcium was fairly evenly distributed between the cortex and the medulla. The renal capsule was thickened.

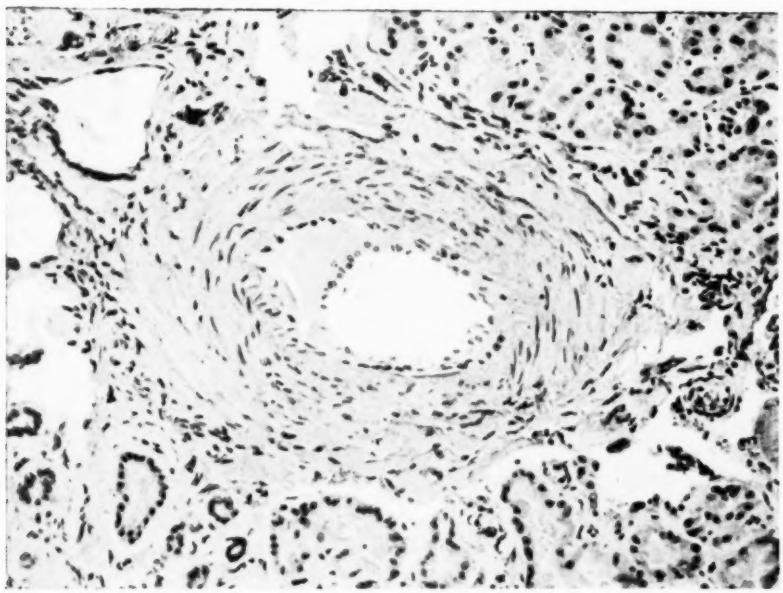


FIG. 7. A high power microphotograph (X 200) of the kidney showing an arteriole with changes fairly characteristic of those seen in the smaller renal branches, namely, hypertrophy of the medial and slight fibrosis of the adventitial coat, without calcification. The appearance of endarteritis is false, and due to partial thrombosis. See also the dilated tubules on the left of the microphotograph.

The suprarenal arteries were grossly diseased but the histology of the suprarenal capsules was not otherwise disturbed. There was arterial degeneration and deposit of calcium in the thyroid and lymphatic glands. One of the parathyroid glands was dissected out; it measured 2-3 mm. in diameter and was histologically normal. There was no evidence of any parathyroid tumour in the neck.

All the long bones showed changes. These were studied in the tibiæ, the description of which will serve for all. There was no bending or other deformity, and no epiphyseal enlargement. The lower epiphyseal line was slightly broadened and irregular. Lying above it was a wide irregular zone of dense calcification, and then alternating bands of osteoporosis and osteosclerosis. Roentgenograms of the long bones taken during life had already given a very clear idea of these changes (Fig. 1).

HISTOLOGY OF TIBIA.—Before describing the histology of this bone a brief outline of the results to be expected from the staining of decalcified bone with hæmatoxylin and eosin will make what follows clearer.

An actively growing and normal metaphysis, decalcified in acids and stained with hæmatoxylin and eosin, is seen to have a narrow epiphyseal line consisting of regular columns of some 10-15 cartilage cells. The older cells in these columns lie towards the diaphysis, and stain blue with hæmatoxylin in association with the calcium recently deposited in their neighbourhood (preliminary calcification). Disturbances in calcium and phosphorus concentration may delay preliminary calcification and provided growth continues, this results in the formation of longer columns, which tend to more or less linear irregularity and stain badly with hæmotoxylin.

Properly formed bony trabeculæ usually stain pink with eosin. It has been suggested that hæmatoxylin does not specifically stain calcium salts but it often

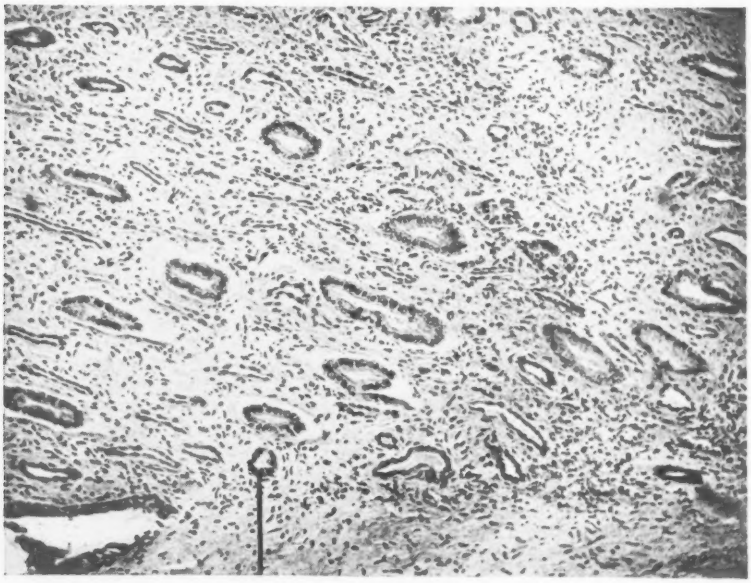


FIG. 8. A lower power microphotograph of the kidney (X 75) showing great interstitial fibrosis, a dilated tubule (at bottom left) and to its right a small deposit of calcium in the cells of a tubule.

identifies areas in which changes favourably to the deposition of calcium are taking place, particularly if iron and mordants, such as aluminium, chromium, etc., are present. The staining reaction, which occurs even after decalcification, probably depends on the special nature of the ground substance in which calcium is deposited, and on the presence of small quantities of other heavy metals[20]. The younger the deposits the more intense the hæmatoxylin stain. This rule also applies to alizarin, a specific calcium stain.

A section of the lower end of the tibia, decalcified in acid and stained with hæmatoxylin and eosin, showed a slightly broad epiphyseal line, containing some 25-40 cells in the cartilage columns. The columns were somewhat irregular and the older cells (those towards the diaphysis) did not take up hæmatoxylin, indicating deficient calcification. Immediately above these cells, and towards the diaphysis,

there was a zone of osteoid tissue, and then a zone of normally trabeculated and well-formed bone in which a very unusual feature was observed, for the trabeculæ were encrusted with a thick layer of calcium (stained blue) clearly outlining the pink structure of each spicule of bone. In addition a few small areas of calcium were to be seen pathologically deposited in the marrow spaces.

Thus strikingly were the radiological, pathological and histological appearances in these bones correlated. But to what purpose? With excessive and pathological deposits, how could it come about that there was insufficient calcium and/or phosphorus to permit of normal preliminary calcification taking place in growing cartilage? To this question we will return later.

Calcium deposits

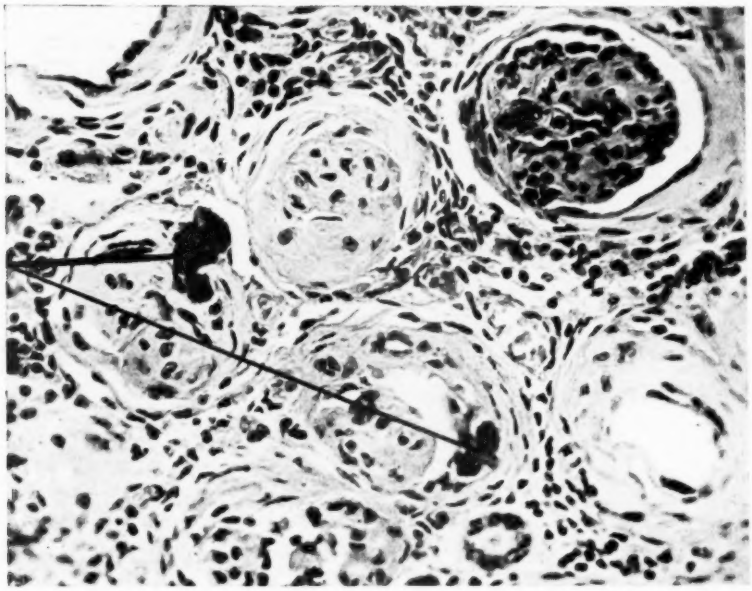


FIG. 9. A high power microphotograph of the kidney (X 300) showing various stages of glomerular fibrosis. Calcium is seen deposited in two of these glomeruli.

Discussion.

This case of stunting with widespread calcification in the tissues and arterial disease, might be provisionally classified as a case of renal dwarfism in so far as there was retarded growth and renal disease. But this takes us no nearer to an explanation of the pathology of the condition, for renal dwarfs are seldom the subjects of extreme arterial disease and seldom, if ever, of calcinosis. We may be forced to leave it an open question whether there was primarily renal or primarily arterial disease in this case, but it is clear that we have to deal with abnormal tissue calcification. If we wish to enquire into the possible causes for the excessive deposition of calcium in a case such as this we must consider the following possibilities.

Chemically there are two factors controlling the precipitation of calcium phosphate, these are the Ca/P multiple and the H ion concentration. An increase in the first or a decrease in the second should bring about an increased deposition of calcium.

Clinically alkalosis does not appear to be of great importance in increasing calcification although an acidosis is undoubtedly of importance in the reverse effect. Variations in the calcium and phosphorus concentation appear to be more important.

The levels of both calcium and phosphorus in the blood can be temporarily increased by suitable feeding methods (e.g. calcium gluconate) but this would not appear to be of long enough duration to produce effects. Both vitamin-D and parathormone are capable of increasing the calcium and phosphorus concentration, and both bring about deposition of calcium in the tissues when given over long periods in excess. This result, however, is dependent on an adequate supply of calcium and phosphorus being obtainable in the diet. On diets deficient in calcium and phosphorus large quantities of parathormone or vitamin-D raise the values for calcium and phosphorus in the plasma, the mineral being obtained by a process of mobilization from the bones. Deposition of calcium in the tissues under these circumstances consists in a transference from bone to tissue.

There is no evidence in this case to determine whether any of the above causes contributed to the condition. On general grounds one would suspect an increased activity of the parathyroids, but not of such degree as would bring about the now well-recognized bony changes. Of this the evidence is entirely negative. In this connection it should be recalled that parathormone has a biphasic effect. Small doses increase the rate of removal of calcium from the blood and therefore increase calcification, while with large doses the stimulus to mobilize calcium is greater than that to deposit and the serum calcium increases. The possibility that this case can be explained on the basis of an excessive intake of vitamin-D seems to have been excluded by repeated questioning of the parents and their medical advisers. At this juncture it may be recalled that lime water began to be administered (a common enough practice) at the age of 8 months. Might a small, but long-continued, excess intake of lime have conduced to high calcium levels in the blood? We think that on account of the amount, duration and date of lime water administration this factor cannot have been more than a contributory one.

It has already been asked how a rachitic state (demonstrated histologically in the growing cartilage) could have arisen in the presence of a more than adequate supply of calcium in the tissues. It is tempting to try to explain this anomaly by assuming a relatively deficient supply of phosphorus. But the single quantitative estimation carried out in hospital showed a somewhat high phosphorus value in the blood (6·68 mgm.) and a diminished Ca/P ratio. The alternating zones of osteoporosis and osteosclerosis described in the tibia suggest some phasic disorder of calcium and

phosphorus metabolism in this case and demand extra caution in the interpretation of the calcium and phosphorus values. It seems that only on these lines is any sort of biochemical explanation forthcoming.

Summary and Conclusions.

The clinical and pathological observations in a case of calcinosis with widespread arterial degeneration, fatal at the age of 2 years and 3 months, are recorded. The ætiology of the arterial disease in this case is quite unknown, nor is its relation to the disordered calcium and phosphorus metabolism understood. An extreme obliterative endarteritis predisposed to local tissue degenerations, and a slightly excessive intake of lime, in the virtual absence of normal bone growth, may have been a factor in the deposition of calcium in the damaged arteries, degenerating tissues, and in the bones. These secondary changes may have been dependent on phasic disturbances in the Ca/P ratio, sufficient to produce pathological calcifications, disordered growth of bone, and latent rickets.

The calcinosis in this case was not due to excessive intake of vitamin-D. Other cases found in the literature, such as those of Bryant and Hale White (1901), Hodgson (1815), and possibly Kennedy (1932), make it clear that there are conditions in childhood, other than hypervitaminosis-D, which can give rise to pathological calcification, and that some of these cases are associated with extreme arterial degeneration. For this rare group the descriptive clinical title of 'calcinosis with arterial degeneration' is suggested.

I should like to acknowledge my thanks to Dr. Robert Hutchison for permission to publish this case, to Dr. W. W. Payne for carrying out the biochemical investigations and for assistance in writing the discussion, to Dr. C. F. T. East and Dr. E. ff. Creed for histological opinions, to Dr. B. Shires for taking the radiograms, and to Mr. D. Martin for the preparation of the histological material and the photographic illustrations.

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A CASE OF SUB-ACUTE INTUSSUSCEPTION WITH SKIAGRAMS

BY

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It is so unusual for a physician to have the opportunity of studying the radiographic appearances of an intussusception that the present case is recorded. The patient was a girl of three years old presenting an obvious

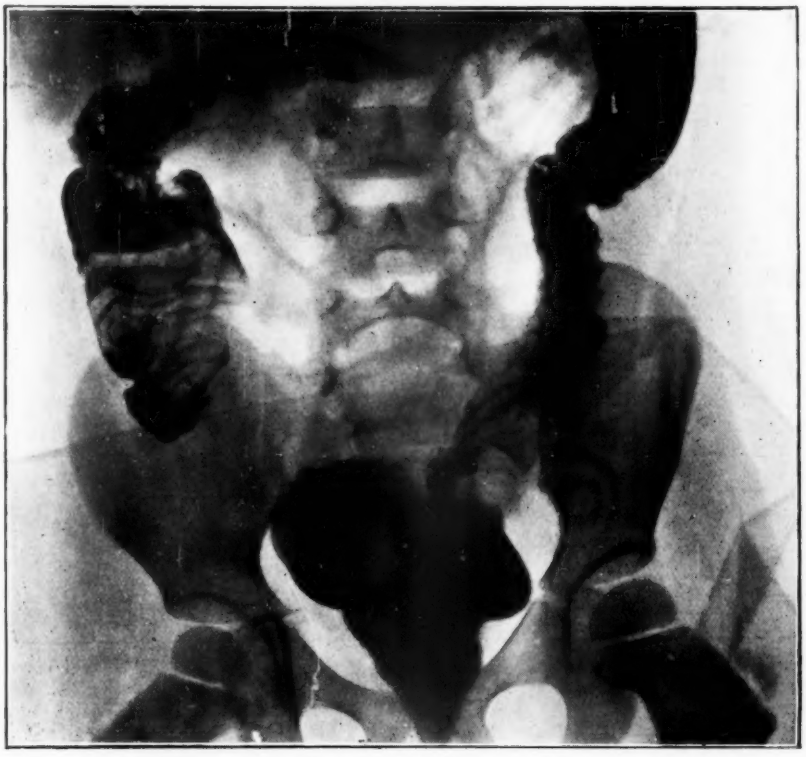

FIG. 1.—Barium enema: immediately after evacuation.

abdominal tumour which was at first regarded as a chronic intussusception. The course of the illness showed, however, that it was more properly classed as sub-acute. It produced at no time any urgent symptoms, and ultimately it disappeared either spontaneously or aided by the bowel wash-outs which were given almost daily. Laparotomy proved that the reduction of the intussusception was complete. A barium enema was given on the seventh day of disease, followed by an opaque meal two days later.

Case report.

Florrie G., aged 3 years and 2 months, was taken with severe abdominal pain and vomiting on April 10th, 1932. She vomited all liquids and had no action of the bowels. No blood or mucus was passed per rectum. On April 13th she was admitted to hospital when she was found to show a smooth rounded mobile tumour in the left side of the abdomen at the level of the umbilicus. This was only slightly tender. No blood or mucus appeared on digital examination of the bowel. An aperient enema was given at once from which there was a large scybalous result, showing traces of blood and a little mucus. The child's general condition was quite good, and immediately after the enema the tumour could not be felt for the time being. During the next three days she was sick only once, and the bowels were open by enema. The chief symptom was that of attacks of severe colic coming on in the region of

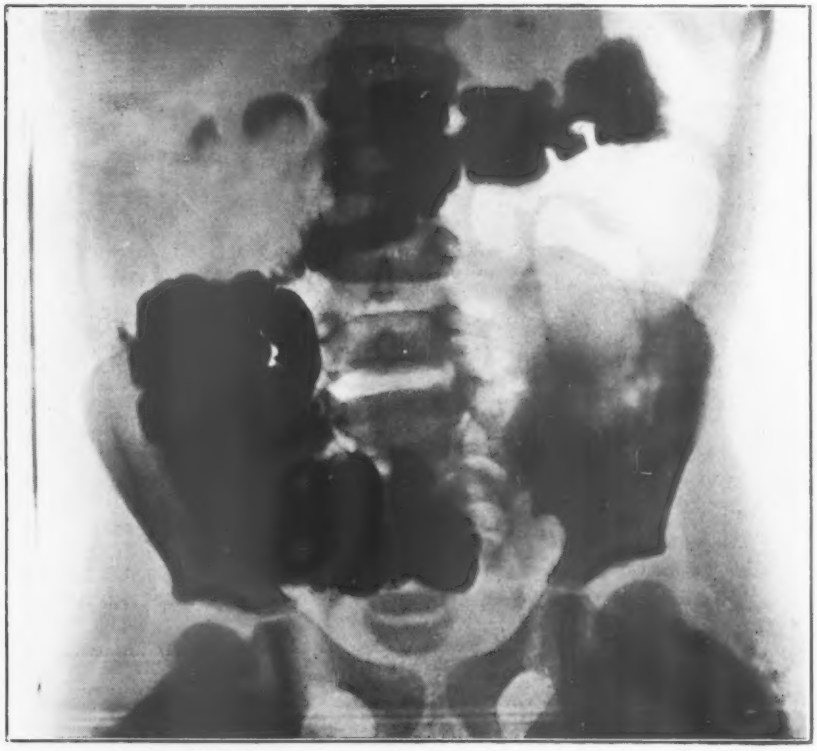

FIG. 2.—Barium meal: at 6 hours.

the tumour at irregular intervals and occurring about six times in the twenty-four hours. The tumour reappeared on the left side, and it was noticed that very shortly after the abdomen had been palpated an attack of pain would supervene. The pain lasted for a few minutes only.

I saw the child for the first time on Saturday, April 16th. She then presented an obvious tumour in the splenic region. Palpation caused the tumour to harden and gave rise to a short attack of colic. It was impossible to mistake the tumour for anything other than an intussusception, and as the child's condition on the seventh day of illness was so good I ordered an immediate examination by means of an opaque enema. The results of this (Fig. 1) clearly demonstrated the presence of an intussusception. As the child kept well an opaque meal was given on April 18th, and the films taken at 6 and 24 hours (Fig. 2 and 3) again show the

condition well. It is noticeable that the intussusception in the skiagrams has travelled back to the right side of the patient. Seen on April 19th it was impossible to be sure of the presence of any tumour, but it was judged to be unsafe to leave the abdomen unexplored for fear of missing an incomplete reduction of the intussusception. On April 20th Mr. Shattock opened the abdomen but found that complete reduction had occurred. The ileo-cæcal region was œdematous and the adjacent glands were enlarged and soft. One of these in the ileo-cæcal angle was removed, the cæcum was stitched to the posterior abdominal wall, and a long healthy appendix was removed. Recovery was uneventful except for some bronchial catarrh.

Radiographic examinations.—Figure 1 is from a film taken immediately after the evacuation of a barium enema. It shows the apex of the intussusception just below the hepatic flexure. The barium has been

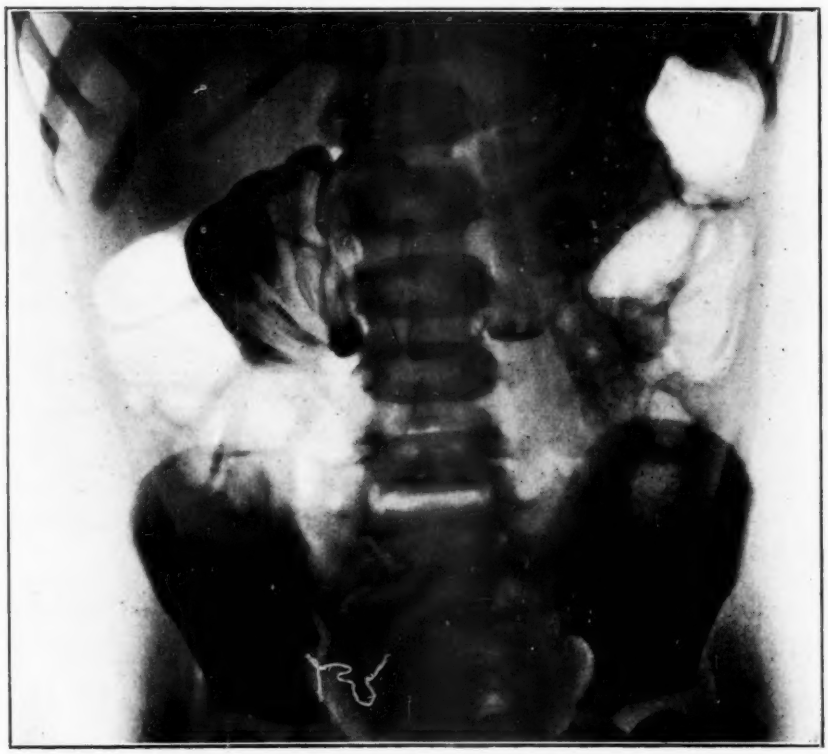

FIG. 3.—Barium meal: at 24 hours.

insinuated between the intussusceptum and the intussuscipiens, clearly showing the folds in the mucosa.

Figure 2 is from a skiagram taken six hours after an opaque meal. It shows ileal stasis and the apex of the intussusceptum at the middle of the transverse colon. Haustration is seen at the upper and lower borders of the intussuscipiens, the clear zone between being occupied by the intussusceptum. The inclusion of the barium at the upper and lower borders only is probably due to the flattening effect of the indrawn mesentery.

Figure 3 is from a film taken twenty-four hours after ingestion of the meal. Practically the whole of the meal has been passed with the exception of a trace which perfectly outlines the apex of the intussusceptum at the extreme left of the transverse colon. The resemblance of this to the cervix and os uteri is well shown.

Discussion.

In the present case the radiographic examination cannot be said to have been of value in the diagnosis of the presence of an intussusception as the tumour gave clear evidence of that condition. It did, however, enable us to watch the gradual reduction of the intussusception, and it might, had it been tried, have been of use in demonstrating that the intussusception had been completely reduced, and so saved the child from operation.

The successful demonstration of the intussusception by an opaque enema raises the interesting question whether such means of diagnosis might not be of considerable value in doubtful and acute cases. It would seem to be worth trying as, at all events in hospital practice, it could be so quickly performed as to lead to no real waste of time. In the present instance examination by screen alone showed satisfactory evidence of intussusception.

Summary and conclusions.

1. An example of a subacute ileo-cæcal intussusception in a girl of three years is described, and skiagrams are reproduced showing the condition by means of a barium enema and an opaque meal.

2. It is suggested that in acute cases of intussusception if there is difficulty in diagnosis, screen examination after an opaque enema might give valuable information without undue waste of time.

The films were taken by Miss Frost, radiographer to the Paddington Green Children's Hospital.

THE TREATMENT OF KALA AZAR IN CHILDREN

BY

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In an earlier number of the Archives[1] the writers gave an account of the clinical symptoms and laboratory findings in cases of kala azar as they had seen it in the children of North China. The following paper is a continuation of the subject, reporting the results, so far as they were ascertainable, of treatment in the same districts.

The efficacy of antimony in the treatment of kala azar was established before the period covered by these observations. China gave antimony to the world[2], but the honour of its successful introduction and application in the treatment of kala azar belongs chiefly to Napier and to Brahmachari of India. The compounds of antimony now in use for the treatment of kala azar are direct results of the careful clinical observations made by these two workers. It is indeed an inspiring story to follow the clinicians and chemists co-operating to eliminate one difficulty after another; until in 1928 Napier[3] could say: 'Thirteen years ago the death rate in kala azar was said to be 95 per cent., whereas now, at whatever stage of the disease the patients first come under treatment, the recovery rate should be at least 95 per cent.' Our own small series of cases illustrates well the strides which have been made since the introduction of tartar emetic for the treatment of kala azar.

The present study is an attempt to collect data, from hospital records and from patients, which may be of use in estimating the value of various antimony preparations in the treatment of kala azar in children. All cases reported in this study showed the presence of Leishmania donovani bodies in films made from puncture of the spleen or liver, or both.

Antimony preparations.—The antimony preparations used for the treatment of the cases reported were:—

TARTAR EMETIC. Potassium antimony tartrate, sodium antimony tartrate and the Burroughs Wellcome preparation of antimony and sodium tartrate, 2 parts, to sodium chloride, 1 part, are included in this group. The

solution, either 1 or 2 per cent., was made in freshly distilled sterile water or sterile saline. A freshly prepared solution was used. Injections were given intravenously every third day, unless there was indication that a longer interval between doses was advisable. In most cases, the initial dose was ½ c.cm., which was very gradually increased. More than 4 c.cm. of a 1 per cent. solution was rarely given. Reactions were not unusual following the use of this drug. The most frequent reaction observed was severe coughing, with expectoration of blood-stained sputum, accompanied by cyanosis, dyspnœa and fever. Such a reaction followed immediately upon the intravenous injection of the drug and all the symptoms except fever passed off within a very short time. Nausea and vomiting were not unusual, either accompanying such attacks as are described above, or alone. If any of the solution escaped into the surrounding tissues during administration, there was immediate acute pain, soon followed by redness and swelling of the area infiltrated, and often resulting in necrosis of the involved tissues.

ANTIMOSAN (Heyden 661). This is a complex salt of antimony oxide and a non-toxic derivative of pyrocatechin. It contains trivalent antimony, about 12·5 per cent.[4] This drug was prepared in sterile distilled water, 5 per cent. solution, and given intravenously, beginning with 1 and gradually increasing to 2 c.cm. It was possible to give the drug on successive days, but in most cases it was given on alternate days.

STIBAMINE GLUCOSIDE. This is an aromatic compound allied to sodium para-amino-phenyl-stibiate, with an antimony content of about 30 per cent. This drug was dissolved in sterile distilled water. In most of the cases, a 2 per cent. solution was used. The injections were given intravenously, beginning with 0·03 grm. of the drug every third day, and gradually increasing to 0·1 grm. in about two weeks. This dose was continued, if no unfavourable symptoms developed, until the total quantity was administered.

STIBOSAN (Heyden 471). This name is given to meta-chlor-para-acetyl-amino-phenyl stibiate of sodium, an organic preparation containing 31 per cent. of antimony[4]. The drug was prepared as a 2 per cent. solution in sterile distilled water, and given intravenously, on alternate days, in doses beginning at ·03 grm. and increasing ·01 for each injection until 0·1 grm. was reached. This quantity was continued, if no unfavourable symptoms developed, until the full amount of the drug had been given.

NEOSTIBOSAN (693). This is an amine salt of para-amino-phenyl-stibinic acid, containing approximately 42 per cent. of pentavalent antimony firmly attached to carbon. After being used for three years, the preparation was so modified in 1927 that it is said to be no longer emetic when administered in large doses. This drug has been used by us in 5 per cent. solution, made up in sterile distilled water. The drug may be given intravenously or intramuscularly. We have given full treatments intramuscularly and have observed no pain or local reaction following the

injections. In a few of our cases there has been nausea immediately following intravenous administration of the drug. The initial dose of drug given is 0·05 grm. which is usually increased to 0·1 grm. at the second injection. This dosage is used for two or three injections, when it is increased to 0·2 grm. for the remainder of the treatment. If the child is in fairly good condition, or if he has noma, the injections are given daily. We have found that children who have diarrhœa or dysentery do not do well with daily injections.

Except in the case of the first-named preparation, a reaction following injection was rare. If it occurred, it consisted in nausea developing soon after intravenous injection of the drug and soon disappearing. A few such reactions have been observed with neostibosan, even during the early course of injections.

We have observed that the few cases treated in our clinic and not admitted to hospital, usually ran a fever to the end of the treatment and did not show as marked early blood repair as patients who enter hospital and remain in bed during the greater part of the time they are receiving the injections.

Diet.—The diet is such an important part of the treatment of kala azar in a child that we feel warranted in outlining the routine diet ordered. The appetite is usually good and, even in the cases where the fever is high, we find that the patients do well on the following diet:—

6 a.m.	Whole milk	6-8 oz.
8 a.m.	Cereal—rice, millet, wheat	4 oz.
	Cornmeal	
	Sugar	1-2 teaspoonsful
	Egg	1-2
	Whole milk	6 oz.
10 a.m.	Cod liver oil	4 c.c.
12 noon.	Liver	2 oz.
	Spinach, carrots or cabbage	4 oz.
	Steamed rice or steamed bread	4-8 oz.
	Baked sweet potato	1
	Sugar	1-2 teaspoonsful
4 p.m.	Liver soup	4 oz.
6 p.m.	Liver	2 oz.
	Steamed rice or other cereal	8 oz.
	Whole milk	8 oz.

For the sake of convenience, the antimony preparations used are designated by letters, as indicated in Table 1. Facts concerning the patients treated by these antimony preparations are arranged in corresponding groups designated A, B, C, D, E, F respectively. Owing to the small number of cases in groups B and F, these groups are not included in the detailed study of the cases. Of the 134 patients in Table 1, 3 were discharged against advice before treatment was finished, and 22 died during the course of treatment.

TABLE 1.
SYNOPSIS OF TREATMENT IN 134 CASES.

Reference letter.	Antimony preparation.	No. of cases.	Date of treatment.
(a) ...	Sodium antimony tartrate	73	July 4, 1921—May 10, 1925
(b) ...	Antimosan, 661 ...	3	Nov., 1924—Feb., 1925
(c) ...	Stibamine glucoside ...	8	Feb., 1926—Nov., 1927
(d) ...	Stibosan, 471	13	Aug., 1924—Dec., 1928
(e) ...	Neostibosan	34	July, 1928—Mar., 1931
(f) ...	(b) + (d) + (e) ...	1	April, 1926
,, ...	(c) + (e)	1	Sept., 1926
,, ...	(d) + (e)	1	Aug., 1924

TABLE 2.
FATAL CASES IN AUTHORS' SERIES.

Primary diagnosis.	Antimony preparation.		
	(a)	(f)	(e)
Bronchopneumonia	7	—	1
Dysentery	1	—	—
Bronchitis	1	—	—
Necrosis around injection	1	1	—
Cancrum oris	2	—	—
Lobar pneumonia	3	1	—
Acute œdema of lungs	—	1	—
Malnutrition	—	1	—
Hookworm disease	—	1	—
Cause not established	1	—	—

Table 2 shows the cause of death in the patients who died during treatment and the antimony preparation used in treating the kala azar,

Table 3 shows the list of diseases complicating kala azar in our series of children. The period during treatment is practically covered by the services of two physicians. The change of physicians was made in 1924. We feel, from our more recent investigations, that the incidence of spirochætal

TABLE 3.

COMPLICATIONS OF KALA AZAR IN AUTHORS' SERIES.

Disease.	Treatment (a)			Treatment (b), (c), (d) & (f)			Treatment (e)		
	before	during	after	before	during	after	before	during	after
Ascariasis	34	—	—	16	—	—	20	—	—
Bronchitis	9	13	4	4	5	—	4	2	—
Bronchopneumonia ...	13	15	13	5	5	5	2	3	—
Cancrum oris	4	5	3	4	3	—	5	4	2
Diarrhœa	4	2	1	—	1	—	1	2	—
Dysentery, amœbic ...	—	—	—	1	—	—	—	—	—
,, bacillary ...	—	—	—	—	—	—	1	1	—
Œdema of lungs, acute ...	—	—	—	—	1	—	—	—	—
Otitis media, acute ...	—	2	1	—	—	—	5	5	2
,, ,, chronic ...	3	3	1	3	3	1	—	—	—
Mastoiditis	—	1	1	—	—	—	—	—	—
Nephritis	2	2	2	1	1	—	—	—	—
Hookworm disease ...	4	2	—	4	4	—	1	1	—
Heart disease, mitral ...	—	—	—	1	1	1	—	—	—
Tuberculosis, hilum ...	—	—	—	1	1	1	—	—	—
,, peritoneal ...	—	—	—	1	1	1	—	—	—
,, pulmonary	1	1	1	—	—	—	—	—	—
Inflammation around injection	—	1	—	—	—	—	—	—	—
Spirochætal infection gums	1	1	1	3	2	1	19	19	19
Syphilis, congenital ...	2	2	2	—	—	—	—	—	—
Lobar pneumonia ...	2	4	—	—	1	—	—	—	—
Cervical adenitis, acute ...	7	8	5	—	—	—	1	1	—
Pyorrhœa alveolaris ..	22	22	15	2	2	2	7	7	3
Caries of teeth	9	9	9	1	1	1	2	1	1

infection of gums and intestinal infection with dysentery bacilli is low in the early histories because, at that time, laboratory routine did not include examination for these two infections.

Results of Treatment.—Observations made on the patients subdivided into various groups according to the preparation of antimony used will now be given. Some illustrative case histories are added.

GROUP A. Taking first the group of cases treated with sodium antimony tartrate the results are shown in the following list and Table 4.

Number of cases treated, 67.
Average age, 8½ years.
Average duration kala azar before admission, 10½ months.
Liver puncture positive L. donovani, 65, 6 not done.
Spleen puncture positive L. donovani, 7, 60 not done.
Average days in hospital, 104.
Total average dose of drug, 0·87 grm.
Average number of injections, 37.
Average number of injections to fall of temperature, 26.
Average amount of drug to fall of temperature, 0·81 grm.

TABLE 4.

RESULTS OF TREATMENT BY SODIUM ANTIMONY TARTRATE.

	Before treatment.		After treatment.		Before:	After:
	Max.	Min.	Max.	Min.	Average.	Average.
Body wt., kgrm. ...	—	—	—	—	19·852	29·503
Size liver, cm. ...	10	0·3	10	0·5	4·5	4
Size spleen, cm. ...	25	1·5	25	0·5	13·5	7·8
Hæmoglobin, per cent.	80	30	90	35	54·1	67·3
Red blood cells ...	4,984,000	1,020,000	5,430,000	940,000	3,965,547	4,234,000
White blood cells ...	12,000	1,100	12,300	600	4,224	6,626,000

Illustrative Case (Group A).—Male, about 5 years of age, ill with kala azar 24 months, spleen enlarged 18 months. The child was treated with one per cent. solution of sodium antimony tartrate intravenously. The initial dose was 0·5 c.cm. The dose was gradually increased to 3 c.cm. near the end of the treatment. Three injections were given each week, excepting the fifth and sixth weeks, when the drug was withheld because of enlarged tender cervical glands. At the end of five months, the patient had received 76 c.cm. of the drug. Reactions following injections were, enlarged tender cervical glands noted above, and an attack of coughing following an injection, when the total amount of 27·5 c.cm. had been given. By the end of the course of treatment the enlargement of the spleen had diminished from 17 cm. to 9·5 cm., the hæmoglobin had increased from 50 to 90 per cent., and the red blood cells from 2,895,000 to 5,760,000. There was a gain in weight of 2·5 kgrm. A letter

and a detailed report written six years after the course of treatment indicated that this treatment had cured the kala azar.

GROUPS C AND D. These groups consist of the cases treated with stibamine glucoside and stibosan 471. The results obtained in these groups are given in the following list and Tables 5 and 6; and an illustrative case from each group is briefly recounted.

	GROUP C.	GROUP D.
Number of cases treated	8	12
Average age	8 years	8 years
Average duration kala azar before admission ...	15 mos.	23 mos.
Liver puncture positive for L. donovani ...	8	12
Total average days in hospital	78	68
Total average dose of drug grams	1·54	1·87
Average number injections	18	22
Average quantity of drug to fall of temperature	0·9	1·2

TABLE 5.

GROUP C: RESULTS OF TREATMENT BY STIBAMINE GLUCOSIDE.

	Before treatment.		After treatment.		Before:	After:
	Max.	Min.	Max.	Min.	Average.	Average.
Body wt., kgrm. ...	—	—	—	—	18·760	20·051
Size liver, cm. ...	9·5	0	6	0	4·7	3·8
Size spleen, cm. ...	18	7·5	11	5·4	12·3	5·4
Hæmoglobin, per cent.	50	27	72	5	38	63
Red blood cells ...	4,592,000	1,984,000	4,752,000	2,440,000	2,915,000	3,916,000
White blood cells ...	8,650	1,060	11,000	5,000	3,832	6,973

TABLE 6.

GROUP D: RESULTS OF TREATMENT BY STIBOSAN 471.

	Before treatment.		After treatment.		Before:	After:
	Max.	Min.	Max.	Min.	Average.	Average.
Body wt., kgrm. ...	—	—	—	—	19·640	21·400
Size liver, cm. ...	7	1	6	1	4·1	2·4
Size spleen, cm. ...	16·5	—	19	3	—	7·3
Hæmoglobir, per cent.	75	18	80	32	48	62
Red blood cells ...	4,950,000	2,448,000	4,900,000	2,500,000	3,655,000	4,130,000
White blood cells ...	9,100	2,450	8,500	3,000	5,380	6,840

Illustrative Case (Group C).—Male, 8 years of age, had been ill with kala azar for 2 years. Spleen first enlarged 18 months before admission. Patient received stibamine glucoside, total gm. 1·92. The drug was given intravenously on alternate days, beginning with gm. 0·03 and gradually increasing to gm. 0·1 at the end of 12 days. This dose was continued until the total amount had been given.

TABLE 7.

RESULTS IN ILLUSTRATIVE CASE IN GROUP C.

	Admission.	End of treatment.	23 months after discharge.	47 months after discharge.
Spleen, enlarged ...	18 cm.	11·5 cm.	6 cm.	0 cm.
Liver, enlarged	6 cm.	4·5 cm.	2·5 cm.	0·5 cm.
Body wt.	22·5 kgrm.	25 kgrm.	—	33·03 kgrm.
Serum globulin test ...	positive.	—	negative	—
L. donovani	Liver positive	spleen neg.	spleen neg.	—
Red blood cells	2,272,000	—	4,512,000	4,900,000
Hæmoglobin, per cent. ...	27	—	68	82
White blood cells ...	1,060	—	5,600	14,050

Illustrative Case (Group D).—Male, about 5 years of age. Patient was brought to hospital by a friend of the family who said the patient had been suffering from afternoon fever for one month, and that the parents of the patient had noticed for one month a mass below the left costal margin. Patient remained in hospital 10 weeks receiving stibosan up to a total of 1·49 grm. The drug was given on alternate days intravenously in 2 per cent. solution. An initial dose of 0·03 grm. was gradually increased to 0·08 grm. near the end of the course. Ten weeks after this treatment was finished, the patient returned to hospital for re-examination. While at home,

TABLE 8.

RESULTS IN ILLUSTRATIVE CASE IN GROUP D.

	First admission.	End first treatment.	Second admission.	End second treatment.	Third admission.
Spleen, enlarged ...	7·5 cm.	6 cm.	5 cm.	4·5 cm.	3 cm.
Liver, enlarged ...	4 cm.	3 cm.	4·5 cm.	2·5 cm.	2·5 cm.
Body wt. ...	18·250 kgrm.	22·850 kgrm.	20,580 kgrm.	22·300 kgrm.	20·300 kgrm.
Serum globulin test	negative	—	negative	negative	negative
L. donovani (spleen)	positive	positive	positive	—	negative
Red blood cells ...	3,032,000	4,364,000	4,950,000	4,824,000	5,100,000
Hæmoglobin, per cent.	48	75	75	75	60
White blood cells...	1,850	3,800	7,600	9,880	7,400

patient had lost kilo 2·270. The spleen was 1 cm. smaller than at time of discharge. L. donovani bodies were found in spleen puncture films. Stibosan was again given as in first course. Because of illness in family, patient was taken home when a total of 0·63 grm. had been given. One month after second discharge, patient returned for examination. Twenty-six months after last visit, a report indicated that patient was completely cured of kala azar.

GROUP E. There remain for consideration the group of cases treated by neostibosan by intravenous and intramuscular injections.

Number of cases treated, 34.
Average age, $7\frac{1}{3}$ yr.
Average duration kala azar before treatment, 12 months.
Liver puncture positive for L. donovani, 27.
Spleen ,, ,, ,, ,, 8.
Average days in hospital, 30.
Total average dose of drug, 1·6 grm.
Average number of injections, 11.
,, ,, ,, ,, to fall of temperature, 9.
,, amount of drug to fall of temperature, 1·47 grm.

TABLE 9.

GROUP E: RESULTS OF TREATMENT BY NEOSTIBOSAN.

	Before.		After.		Before.	After.
	Max.	Min.	Max.	Min.	Average.	Average.
Body wt., kgrm. ...	—	—	—	—	17·717	19·160
Size liver, cm. ...	8	0	10	0	4	4
,, spleen, cm. ...	17	5	17	0	11·8	8
Hæmoglobin, per cent.	78	17	80	40	43·8	59 3
Red blood cells ...	4,448,000	1,056,000	5,728,000	2,025,000	3,014,521	3,530,900
White blood cells ...	14,000	1,400	10,800	2,500	4.826	6,005

Illustrative Cases (Group E).—(1) Female, 3 yr. 2 months of age. Ill with kala azar 7 months before admission; spleen enlarged 5 months. During first stay in hospital, patient received neostibosan intravenously, total dose of 1·6 grm. Doses of 0·1 grm. were given on successive days, except the third day when 0·2 grm. was given. There was no reaction following the injections. One month after treatment was finished, patient returned for observation and it was found that the spleen had enlarged during the interval. At this time a second course, total amount of neostibosan 0·5 grm. was given intravenously. A letter written 20 months after the last injection indicated that the patient was completely cured of kala azar.

(2). Male, 8 years of age, ill with kala azar for 12 months. Spleen had been enlarged for about one year. Patient received intramuscular injections of neostibosan, a total of 1·7 grm. The drug was administered in doses of 0·1 grm. first day in hospital and 0·2 grm. on alternate days, until the full amount had been

given. At the first return visit no treatment was given for kala azar. Patient was again brought back for second return visit because he was pale and did not gain strength. A written report 13 months after the second treatment was finished indicated that the kala azar had been cured.

(3). Male, 6 yrs. 11 months of age. Ill with kala azar 15 months. Spleen enlarged 12 months. Patient received intravenous injections of neostibosan gm. 0·05 for three successive days at beginning of treatment and then, gm. 0·2 daily until a total of gm. 1·75 was given. A letter received 13 months after treatment was finished indicated that the patient was cured of kala azar.

Discussion.

In discussing the efficacy of antimony preparations in treatment of kala azar and in estimating the proper total amount of the drug to be given, physicians agree that it is not possible to depend on any one laboratory or clinical finding as evidence that the patient is cured of kala azar. Films and cultures made from spleen and liver punctures may be negative while the patient still harbours Leishmania donovani in his body. While positive cultures indicate that the patient still harbours the infection, negative films and cultures have been found in cases which later showed that the patient was not cured of kala azar. It has been a constant finding in our cases that tests for serum globulin changes characteristic of kala azar are positive in cured cases for several months following completion of treatment with antimony. Taken in order of time, the clinical signs indicating improvement following treatment of kala azar with antimony are: (a) Cessation of fever; (b) increase in body weight; (c) reduction in size of spleen and liver; (d) increase in total leucocyte count; (e) increase in red cell count and hæmoglobin; (f) physical appearance of well being.

In cases which we have been able to follow we have found that, if the above clinical manifestations are maintained for two months after the course of antimony is finished, the patient is cured. The cases which have returned with recurrence report that, at the end of a month, there are recurrence of fever and renewed enlargement of the spleen. As our cases return to the endemic area where they contracted the disease, the possibility of re-infection has to be taken into account. This is an important question which, as far as we know, has not been investigated: does infection with L. donovani produce a lasting immunity after the kala azar has been cured?

In all cases, the parents are requested to bring the child back for re-examination one month after the antimony treatment is finished. A few return for this examination, but very few return for any later examination. It is the consensus of opinion of co-workers, who know the habits of these parents, that failure to return indicates that the patient is free from symptoms from which he originally sought relief. We of the West who do not appreciate fully the effort put forth in making a long country trip in China may be prone to doubt this statement. The unanswered requests for written reports on the condition of patients may be accounted for by the

fact that the majority of the parents cannot read or write, and to secure the services of a writer often entails expenditure of time and money.

According to written reports and return visits for examination, we would tabulate known cured cases as in Table 10. All cases included in this report had finished their treatment at least six months before the report was written or the examination reported was done.

TABLE 10.

END RESULTS OF TREATMENT.

Antimony preparation.	Number of cases.	Av. years after last treatment.	No evidence of kala azar.	
			Examination.	Letter.
(a)	15	7	0	15
(c)	6	4	0	6
(d)	6	3½	—	6
(e)	23	1½	6	23
(f)	6	5½	0	6

Cases known to be cured of kala azar, a total of 56 out of 134 who completed treatment.

Conclusions.

1. Antimony preparations in treatment of kala azar: Sodium antimony tartrate, antimosan, stibamine glucoside, stibosan and neostibosan will cure kala azar in children. It requires a long time for completion of a full course of tartar emetic. Reactions to the drug are frequent and there seems to be a direct relation between the use of this drug and the frequent occurrence of bronchopneumonia during a course of treatment with the drug. Of the other named antimony preparations, neostibosan requires the shortest period for administration of the full course. It can be administered intramuscularly without any untoward symptoms. The only reaction to this drug has been a very occasional nausea immediately following the injection.

2. Complete rest in bed, with proper diet, is necessary during treatment, if the optimum relief from clinical manifestations of kala azar is to be secured early.

3. The only criterion of cure in kala azar at present available is the gradual disappearance and continued freedom from symptoms and signs of the disease during and following the treatment.

We wish to express our thanks to Dr. E. B. Struthers for the privilege of allowing us to review the cases treated prior to 1924 and for his kindness in providing us with neostibosan before the drug was placed on the market.

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BRITISH PÆDIATRIC ASSOCIATION.

PROCEEDINGS OF THE FIFTH ANNUAL GENERAL MEETING.

The Fifth Annual General Meeting was held at the Old England Lake Hotel, Windermere, on Friday and Saturday, the 27th and 28th May, 1932.

FIRST SESSION (MAY 27TH, 10 A.M.).

Business Proceedings : The President, Dr. F. John Poynton, was in the Chair. and there were present 48 members.

The minutes of the last meeting were read and approved.

Letters of regret were read from Doctors Vining, Craig, and Tallerman.

Doctors G. F. Still and Edmund Cautley (both past Presidents) were elected Honorary Members.

President : Dr. A. Dingwall Fordyce was elected President for 1932-33, and the election of Officers and Ordinary Members followed, as recommended by the Executive Committee.

Secretary : Dr. Donald Paterson (re-elected).

Treasurer : Dr. H. Morley Fletcher (re-elected).

Representative for Scotland : Dr. Geoffrey Fleming, in place of Dr. Charles McNeil (Retired under Rule 4).

Ordinary Members : Dr. W. R. Collis of London, Dr. A. G. Ogilvie of Newcastle. and Dr. A. Hayes Smith of Bradford, were elected Ordinary Members.

Next Meeting : The selection of the next place of meeting was left to the Executive Committee, but on a show of hands, it was decided by 15-8 that a meeting should take place next year.

The Treasurer's report was received and adopted.

Change of Rules : Dr. Morley Fletcher moved that Rule 2 be amended to read ' who shall be distinguished pædiatricians practicing in the Dominions and Colonies.' The matter was referred back to the Executive Committee. It appeared that most members were in favour of the term ' Honorary Members ' including distinguished pædiatricians from overseas, and foreign pædiatricians, while some new name such as ' Emeritus Members ' was suggested for those now termed ' Honorary Members.'

1. DR. A. MONCRIEFF (London): ' The economics of the unnatural feeding of Infants.' He said that in Germany, and generally in Europe, cow's milk costs half what it does in England, and since raw milk is never given to children in Germany, surgical forms of tuberculosis are very rare there. A consideration of the milk problem in this country forces the conclusion that our complicated system of grading cow's milk is an attempt to make the public pay for a purity which is largely unreliable, since even certified milk has given rise to severe infections. A comparison of the costs of ordinary cow's milk, special children's milk, and dried milk, in various parts of the world, shows that a baby aged six months can be safely fed in Germany for 1s. 5½d. per week, while in England, a so-called safe method of feeding costs in children's milk, or dried milk, about 5s. 0d. per week. It is suggested that pædiatricians ought to adopt a definite policy about milk, *e.g.*, the abolition of all grading, and concentrate on a good quality ordinary milk to be boiled for children. The cost of dried milk would then have to come down, in order to come into line with this single brand of ordinary liquid milk. At present the cost is about double or more on a basis of reconstitution.

2. Dr. Noah Morris (Glasgow): 'The role of phosphorus in the pathogenesis of infantile tetany.' He said that determination of the calcium and phosphorus retentions of a child with active rickets and tetany for one week before, and for five weeks after the administration of Vitamin D showed that there was no excess retention of phosphorus during the period of tetany. Administration of phosphorus in the form of either the acid or alkaline phosphate, to young children who had rickets or osteoporosis, led to a large excess retention of phosphorus over calcium without the appearance of any signs of tetany. There is, therefore, no support for the view that excess retention of phosphorus is of importance as a factor in the production of infantile tetany.

3. Dr. A. C. Hampson (London): 'The treatment of cerebro-spinal meningitis.' A method was described for the treatment of those cases of cerebro-spinal meningitis in which there is an internal hydrocephalus associated with a 'dry tap' on lumbar and cisternal puncture. A double cannula is introduced into the posterior horn of one laterial ventricle: one tube provides an inflow of irrigating fluid, the other, the out-flow, is connected to a vessel which can be fixed at a given height, thus controlling the pressure in the ventricles. In seven cases, after four days, the flow of C. S. F. was re-established; in four of these cases, the patient made an apparently complete recovery.

4. Dr. Lightwood and Dr. F. John Poynton (London): 'A clinical study of paraplegia of neoplastic origin in childhood.' The clinical and pathological details of four cases of paraplegia due to secondary neoplastic involvement of the spinal cord were used in illustration of the diagnosis difficulties encountered in this condition. Two of the cases were mediastinal sarcomata, one was cervical sarcoma of unknown origin, and the fourth an instance of adrenal neurocytoma showing very unusual features. The sudden onset of the paraplegia in such cases, and its frequent flaccid character, were made the subject of comment. Spinal caries is the usual differential diagnosis, and mimicry may be close. One of the cases resembled tuberculous meningitis.

5. Dr. Hugh T. Ashby (Manchester): 'A case of rickets, congenital syphilis and achondroplasia in the same child.' This case is described on page 231 of the present issue.

6. Dr. C. P. Lapage (Manchester): 'The treatment of chronic hydrocephalus in infancy.' He described cases of chronic hydrocephalus treated for years with gentle compression by a rubber cap. The cases did not essentially need drainage, the slowly increasing circumference of the head being due probably to hyper-secretion. Compression altered the shape of the skull, making it higher and more presentable in appearance, and may have assisted in the slow arrest of hyper-secretion with closing of fontanelles. It was fully recognized that spontaneous cure may take place.

The children who are mentally normal are now learning to walk, and balance their unusually large heads.

7. Dr. Robert Collis (London): 'Hæmolytic streptococci and acute rheumatism. He briefly summarized the facts which had led Dr. Sheldon and himself to conclude that the hæmolytic streptococcus plays an integral part in the ætiology of acute rheumatism. He then described various experiments dealing with the cutaneous reactions of rheumatic patients, and normals, to different products of the organism, viz., the Dick or exotoxin, and an extract of the dried bodies of the organism or the endotoxin. He showed various statistical tables giving the results of such skin tests on a large number of cases. The following points were brought out:—(1) Age is an important factor influencing the reactivity of all children when grouped together. (2) When the rheumatic children are separated from the general group they are found to give many more positive reactions than the controls. (3) Recentness of the last acute rheumatic attack is a most important factor influencing the reactivity of rheumatic cases.

8. Dr. D. W. Winnicott (London): 'Growing pains; the problem of their relation to acute rheumatism,' outlined his opinion that growing pains are of little help in the attempt to diagnose liability to rheumatic heart disease. They occur commonly in children who find life difficult, whose sleep is imperfect, and who are chronically excited or anxious or mentally exhausted, and it is just these children whose hearts overact during physical examination, and who have a labile temperature and an unstable vaso-motor system. It is a grave though common mistake to keep such children in bed, and to foster in them a carefulness about health.

9. Dr. C. D. S. Agassiz (London): 'Tuberculous laryngitis in children.' He stated that this condition is seldom recognized, as the symptoms are seldom severe, and may be absent. There is usually slight uskiness or loss of voice. Dysphagia rarely occurs. Laryngological examination shows pallor and greyish heaped up deposits in interarytænoid region, with or without swelling of arytænoids, or swelling of false cords or puffiness and injection of cords, or even ulceration and deformity of the cords. This condition occurs usually in older children, but may occur in children of 8 or 9 years of age, and nearly always in cases of pulmonary tuberculosis, whose sputum contains tubercle bacilli. In these cases the incidence appears to be high—about 20 per cent. In a recently examined series, the incidence was as high as 27 per cent. (13 out of 48 cases examined.)

Second Session (May 27th, 8.30 p.m.).

10. Dr. W. Sheldon (London): 'Amyoplasia Congenito' with cinematograph. This case has been published in full in the 'Archives of Disease in Childhood,' June, 1932, p. 117.

11. Dr. K. D. Wilkinson (Birmingham) showed cinematograph pictures of interesting medical cases.

12. Dr. R. Hutchison (London) opened a discussion on 'The present state of the teaching and study of pædiatrics in the British Medical Schools, and the means and methods of improvement, and the advisability of instituting a Diploma of Pædiatrics.' He said that although instruction on the subject had greatly improved in recent years, there was still room for further improvement. Every teaching school should have a pædiatric department, but whether it was staffed by 'pure' pædiatrists, or not, did not much matter, provided the teachers were keen and well informed on the subject. Out-patient teaching he considered the most valuable, but it must be systematized, cases being scheduled for teaching purposes, and an hour devoted to them twice a week. Ward teaching was, in his opinion, less valuable, but it enabled students to follow the progress of cases, and to study them in greater detail. There should be two ward demonstrations a week. Lectures were of use for dealing with general principles, e.g., of infant feeding, and for some special diseases, and pathological matters. There might be two lectures a week. In a three months' course, these different forms of teaching would amount to 60 hours in all, but of course, the student must supplement this by reading. An American Committee, which had recently investigated the question, recommended 200 hours of pædiatric instruction, but this seemed unnecessary if the student came to the subject late in in his career, and already well trained in clinical methods. In ordinary post-graduate training a course of a month's duration seemed to be the ideal, but the teaching needed to be carefully planned. Intensive courses threw a great strain on the teaching staff.

As regards the question of a Diploma in Pædiatrics, he had an open mind. It might be of use to men entering the Public Services, e.g., to School Medical Services, Welfare Work, etc., and also for students from the Dominions who wished to have something to show for their post-graduate work. He did not think, however, that it would be easy to get a Diploma instituted. As regards their taking an interest in the study of pædiatrics amongst undergraduates, the chief desideratum was that the subject should be a compulsory one in the final examination.

He was followed by Dr. Charles McNeil, who gave details as to the scope and duration of the teaching of pædiatrics in the University of Edinburgh. After mentioning the defects, he suggested the following improvements:—The insertion of appropriate teaching in the earlier subjects of chemistry, anatomy, physiology, and pathology; an extension of the period of clinical study; more attention to the subject of health and its preservation in childhood, and an examination test on the subject.

Many members took part in the discussion. It was unanimously decided that the first step to improve the teaching was to institute an examination in pædiatrics in the final examination of the students. Four resolutions were then agreed to, and these were to be forwarded to the General Medical Council by Dr. Still and the President, Dr. F. John Poynton. These resolutions urged the instituting of an examination in pædiatrics in the student's final examination.

Third Session (May 28th, 10 a.m.).

13. Dr. E. Pritchard (London); 'Aluminium Poisoning.' Dr. Pritchard drew attention to the possibly poisonous effects of aluminium when food is cooked for infants or children in saucepans made of this metal. He had come across several cases in which he thought he could trace symptoms to this source, when infants had consumed for some time bone and vegetable broth prepared, and sometimes repeatedly re-sterilized in aluminium saucepans. The acute symptoms were diarrhœa, although the chronic effects appeared to be of an opposite nature, resulting in constipation. The symptoms corresponded to those described as resulting from the administration of large doses of aluminium to animals.

14. Dr. A. V. Neall and Dr. J. C. Hawksley (Birmingham): 'Anæmia occurring in both mother and child.' They stated that deficiency of hæmopoietic factors, particularly iron, in the diet of the mother, may cause the appearance of an anæmia in the mother and child at or shortly after birth. In different cases, the shortage may effect the mother, child, and perhaps twin, in different ways, one, two, or all three being affected in different cases. All combinations and permutations occur as shown in the appended list. These cases all show improvement and cure if treated with inorganic iron, which is accelerated by the addition of a yeast preparation (Yestamin).

Mother ...	N	N	N	A	A	A
Child	N	A	A	N	A	A
Twin	N	N	A	N	N	A

A = Anæmic. N = Normal.

15. Dr. Leonard Parsons and Dr. J. C. Hawksley (Birmingham): 'The role of yeast in the treatment of anæmia.' In discussing this subject they first reviewed shortly the recent outstanding advances in the treatment of nutritional anæmias, then pointed out that nutritional anæmia could be cured in some instances by iron, in other by iron and yeast, or iron and copper, and that in some cases all the factors were required. Experimentally and clinically they had found that yeast produced a rise in hæmoglobin, and a reticulocytosis. Finally, the possible factors in yeast responsible for these changes were discussed, and the results of experiments to determine the essential factors were described.

16. Dr. Bernard Schlesinger (London): 'A rare case of amaurotic idiocy with histological sections of the brain prepared by Dr. J. G. Greenfield.' He discussed a case of late infantile amaurotic idiocy, and pointed out how this case served as a link between the usual type of amaurotic idiocy, with cerebro-macular degeneration, as originally described by Sachs and Tay, and Batten, and other

similar forms of cerebral degeneration occurring later in childhood. Dr. Schlesinger's case was not in a Jewish child, and did not show the cherry red spot on the macular, although primary optic atrophy was present. The pathological lesions were distributed over most parts of the brain and cerebellum, and also involved the spinal cord. Both the white and grey matter were affected. Microphotographs from histological sections, prepared by Dr. J. G. Greenfield, were shown. Changes in the brain peculiar to this group of cerebral degeneration were demonstrated. Swelling of the dendrites, the lipoid infiltration of the Betz cells, with displacement of the nucleus, were particularly well seen.

17. Dr. George Bray (London) introduced by Dr. D. Paterson: 'A note on the causation of papular urticaria.' He said that condition forms at least 10-20 per cent. of all skin out-patients at Children's hospitals in England, very few children escaping it in some degree. 80 per cent. of cases commence before the third year, and 95 per cent. before the fifth, and ordinarily it disappears before the age of puberty. Practically all cases are confined to the warmer months of the year, and males and females are equally affected. Many hypotheses have been expounded as to its ætiology, and include disorders associated with dentition or digestion; an ill-effect of vaccination; the result of bad clothing, uncleanliness, or the decomposition of sweat; the result of flea, louse or bed-bug bites or worm infestations; and finally an allergic reaction to environment. As the result of the investigation of 200 cases, Dr. Bray suggested that two factors were involved; one food, the other thermal. The food factor was associated with the assimilation of fats, the most common being those of the pig, and certain edible vegetable oils. Their ingestion generally preceded an attack; their withdrawal generally led to the disappearance of the lesions; with their addition, the lesions could be made to reappear; and many cases gave positive skin tests to specially prepared fatty extracts. Oleic acid, a common constituent of these fats, injected in minute amounts into normal skins, produces an immediate wheal followed by an inflammatory papule which persists for many days. The other factor concerned is heat, and explains why the lesions appear in the warmer months, whilst in bed at night, after warm baths, excitement, exertion, or any of the several febrile illnesses that are common during childhood.

18. Dr. J. d'Ewart (Manchester): 'The use of Avertin as a basal anæsthetic in children.' Dr. d'Ewart recounted his experience in the administration of Avertin as a basal anæsthetic for children in 2,256 cases, stating that his main object was the prevention of the horror of the child occasioned by the administration of an inhaled anæsthetic, at the ritual of the theatre, and unpleasant after-effects of inhalation anæsthetic. These requirements had been met satisfactorily with no deaths, and very few scares, though these occurred occasionally in the early cases of his series.

Emphasis was laid on the extreme necessity of careful preparation and administration of the drug, quietness and sympathetic gentle handling prior to administration being essential. Idiosyncrasy was mentioned, and possible deterioration in the drug on keeping.

ERRATUM.

Page 120. It is regretted that in Dr. Wilfrid Sheldon's article on Amyoplasia Congenita in the last issue, the descriptions of Figs. 4 and 5 were wrongly placed. They should be transposed.

RICKETS, CONGENITAL SYPHILIS AND ACHONDROPLASIA IN THE SAME CHILD

BY

HUGH T. ASHBY, M.D., F.R.C.P.,

Physician to the Royal Manchester Children's Hospital.

The case here reported is of interest as showing evidence of three different diseases, rickets, congenital syphilis and achondroplasia, making the signs and symptoms difficult to interpret correctly.

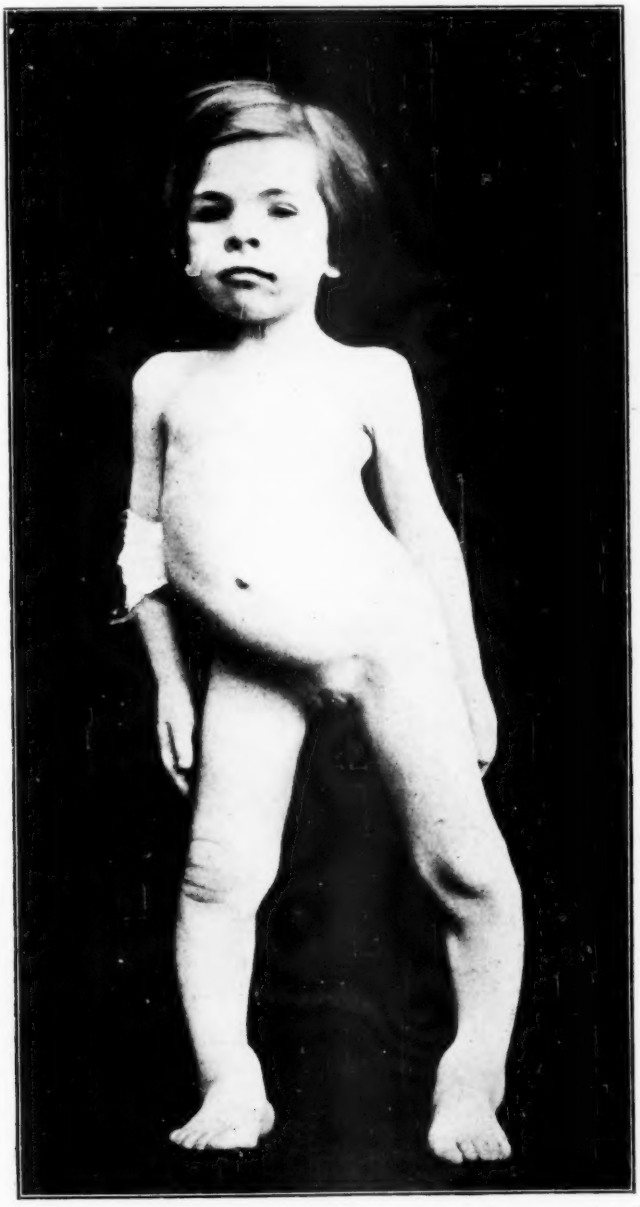

FIG. 1. Girl, age 7½ years, showing rickets and congenital syphilis.

The patient is a girl aged 7½ years, admitted to the Royal Manchester Children's Hospital with a diagnosis of achondroplasia. At first sight this diagnosis is apparently mistaken, as her stature in no way resembles that of achondroplasia. The photograph (Fig. 1) shows that the limbs are in right proportion to the trunk.

She is an only child, though there were two miscarriages previously, and she shows unmistakable signs of congenital syphilis, fissuring of the lips, circumoral eczema, depression of the bridge of the nose, etc. There are,

FIG. 2. Tibiæ showing achondroplasia.

however, no specific bone lesions, except perhaps some slight periostitis of the humeri. There are no sabre tibiæ. The Wassermann reaction was strongly positive and remained so in spite of intensive anti-syphilitic treatment. The blood from both parents was also positive.

The child is also markedly rachitic showing definite epiphysial changes and deformities due to rickets. She is short in stature and there is a congenital scoliosis of the spine.

The radiograms (Fig. 2) are interesting as they show the peculiar condition of the upper ends of the tibiæ. Here there is dense bone with clear cut edges. The bones are lipped and exactly like those of achondroplasia. She is probably an example of a type of achondroplasia not often met with or recognized, as the common type of this disease causes bone changes throughout the body in certain directions. The child also shows no outward signs of achondroplasia, although she was admitted with this diagnosis. The upper ends of the tibiæ are certainly not syphilitic or rachitic.

The difficulty in the interpretation of the radiograms in this case is that the bony changes are not typical of any one disease and are probably the result of more than one cause.